IMPROVED ESTIMATES OF RISK OF EXPOSURE TO PATHOGENS TRANSMITTED BY MOSQUITOES

BY

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DISSERTATION

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ABSTRACT

The exposure of humans to mosquitoes that carry infectious pathogens is a central component to assess the risk of people becoming infected with the pathogen and succumbing to a range of illness. Mosquito-borne illnesses are increasing, but the understanding of the effect of exposure to mosquitoes on the variability of risk has not always been clear. The risk of exposure to mosquito-borne pathogens is complicated by the transmission cycle of the pathogen, the dynamic nature of conditions that affect mosquito abundance and species- and regionally-specific mosquito biting behavior. In the United States, West Nile virus (WNV), transmitted by several species of *Culex* mosquitoes, has been the leading cause of mosquito-borne illness in the United States since its first introduction in 1999. The state of Illinois first encountered West Nile virus in 2001, and the first human cases were reported in 2002. The state has seen significant spatial and temporal variation in WNV cases since then. The overall objective of this dissertation work was to improve our understanding of spatial variability of risk for transmission of WNV to humans. We exploited long-term data on mosquito collection and testing, human WNV illness, weather, landscape, and demographic factors, and used statistical and geospatial approaches to address questions related to the factors that drive vector mosquito abundance, mosquito infection, and human WNV illness. We evaluated the local weather and landscape factors associated with *Culex* abundance first independently, and later used multilevel modeling approach to evaluate the joint effects and weather and landscape when both are analyzed together. We hypothesized that the estimates of mosquito abundance are affected by the trapping methods used to capture them, and we considered the degree to which this factor needs to be taken in to account when analyzing mosquito abundance data. Further, we developed weather based weekly prediction models for the WNV mosquito infection rate (MIR) for the state of

Illinois and nine climate divisions. We observed that the MIR model performed better for northeastern Illinois where intensive mosquito surveillance is carried out compared to southern parts of the Illinois. Finally, we determined the fine-scale dynamic drivers of spatiotemporal variability in human WNV cases in the Chicago region. Using mixed-effects multiple logistic regression analysis, we identified that hot and dry weather conditions and higher mosquito infection rate in preceding weeks were the main drivers of spatiotemporal variability of human WNV illness in Chicago area, with some demographic and landscape characteristics contributing to it. In conclusion, our study helped to understand several essential factors associated with vector mosquito abundance, WNV mosquito infection, and human WNV illness, thus improving our understanding of the risk for pathogens transmitted by mosquitoes at fine geographical and temporal scales. We also demonstrated that the long-term surveillance data on mosquito data and human illness data coupled with publicly available weather, landscape, and demographic data can be successfully used to understand the drivers of disease and to develop prediction models. The knowledge we gained from our approach can be extrapolated to understand the spatial epidemiology of other mosquito-borne diseases, such as St. Louis encephalitis, dengue and chikungunya.

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CHAPTER 1: INTRODUCTION

1.1. BACKGROUND

More than half of the world's population is at risk from one or more vector-borne diseases (WHO, 2014). Some examples of these diseases include malaria, dengue, Zika, chikungunya, West Nile fever, yellow fever, Japanese encephalitis, Lyme disease, Rocky Mountain spotted fever, Chagas disease, scrub typhus, and leishmaniosis (More et al., 2017). Though the burden of vector-borne diseases is higher in developing countries in tropical and sub-tropical regions, middle income and developed countries are also facing threats from emerging and re-emerging vector-borne diseases (Gubler, 1998). For example, Brazil and several other South American countries experienced severe outbreaks of illness from the mosquito-borne Zika virus in 2015 (Rodriguez-Morales, 2015; Gatherer and Kohl, 2016; Heukelbach et al., 2016). In the United States, Lyme disease, a tick-borne disease, and West Nile fever, a mosquito-borne disease, are the leading causes of vector-borne illness (Petersen et al., 2013a; Eisen et al., 2017). Roughly, 30,000 cases of Lyme disease and several hundred cases of West Nile virus infection are reported annually to the Centers for Disease Control and Prevention (CDC) by state and local health agencies (CDC, 2016).

The major vectors capable of transmitting diseases of public health concern include several species of mosquitoes, ticks, fleas, sandflies, flies, and mites (World Health Organization, 2014). Among these different vectors, mosquitoes are widely considered to be the deadliest vector because of their involvement in the transmission of some of the diseases with the highest global burden such as malaria, dengue, Zika, and chikungunya (Kamerow, 2014). Different species of mosquitoes are involved in transmitting these different diseases. For example, *Aedes aegypti* and *Ae. albopictus* are the primary vectors for the transmission of dengue, Zika, and chikungunya virus (Kraemer et al., 2015). Likewise, several species of *Anopheles* mosquitoes are involved in the transmission of malaria (Coetzee et al., 2000). For West Nile virus, it is primarily *Culex* mosquitoes that transmit the virus in North America (Andreadis 2012).

The exposure of people to infectious vector mosquitoes is central to people being infected with particular pathogens. However, the risk of exposure to mosquito-borne pathogens is complicated by the transmission cycle of the pathogen, the dynamic nature of conditions that affect mosquito abundance and species- and regionally-specific mosquito biting behavior (Lambin et al., 2010a; Chaves et al., 2011; Andreadis, 2012; Smith et al., 2014). Human decisions and behaviors are also important, with actions that range from mosquito abatement practices to the use of screened windows, bed nets, mosquito repellents and the avoidance of outdoors activities. Mosquito-borne illnesses are increasing worldwide (Wearing et al., 2016), but the understanding of factors that affect the variability of exposure to mosquitoes has not always been clear.

West Nile virus, a single-stranded RNA virus, belongs to the Flavivirus genus in the family *Flaviviridae* (Grubaugh and Ebel, 2016). This virus is carried by vector mosquitoes and maintained in nature through the mosquito-bird-mosquito cycle (Campbell et al., 2002). In the United States, West Nile virus (WNV) was reported for the first time in New York in the summer of 1999 (Nash et al., 2001). The spread of this disease in the conterminous US was so rapid that human cases of WNV were reported from almost all states in less than a decade after its introduction (Kramer et al., 2008). The availability of already established competent vectors, abundant and diverse bird communities, a naive human population, favorable weather, and optimal landscape conditions all contributed to the rapid spread of WNV in the U.S. (Lambin et al., 2010b; Kilpatrick, 2011). Birds help in the natural amplification of the virus (Hamer et al., 2009), but with varying degrees of competence depending upon the species of bird. The most competent bird species for WNV amplification in the U.S. include the American crow (*Corvus brachyrhynchos*), Blue Jay (*Cyanocitta cristata*), American Robin (*Turdus migratorius*), Common Grackle (*Quiscalus quiscula*), House Finch (*Carpodacus mexicanus*), and House Sparrow (*Passer domesticus*) (McLEAN et al., 2001; Komar et al., 2003; Kilpatrick et al., 2007). The amplification of the virus in particular species of birds coupled with a shifting pattern of mosquito feeding behavior from birds to mammals in the late summer may create an environment for the sporadic spillover events to mammalian species such as horses and humans which results in local outbreaks of illness. Both humans and horses are dead-end hosts and do not contribute to future cases of illness (Kilpatrick et al., 2007; Murray et al., 2010). In humans, more than 80% of the infections do not show any symptoms while nearly 20% develop West Nile fever. In less than 1% of the population that develops West Nile fever, a neuro-invasive form of the disease occurs which can result in death (Sejvar et al., 2003).

In the United States, more than 96% the WNV positive pools of mosquitoes are from a relatively small number *Culex* mosquito species (Andreadis, 2012). The major species involved in WNV transmission are *Cx. pipiens, Cx. restuans, Cx. tarsalis,* and *Cx. quinquefasciatus* depending upon the region (Andreadis, 2012). Generally, in the United States, *Cx. pipiens* and *Cx. restuans* are involved in transmission in the northern and eastern regions, *Cx. tarsalis* is in the western, and *Cx. quinquefasciatus* is in the southern region of the US (Andreadis, 2012). In our study area, in the north central state of Illinois *Cx. pipiens* and *Cx. restuans* have been identified as a bridge vector to transmit WNV infections to humans (Hamer et al., 2008a).

The life history of mosquitoes includes both aquatic and terrestrial stages. The egg, larval, and pupal stages are aquatic while the adult stage is terrestrial. Because of this strong aquatic requirement, weather and landscape conditions influence their life history. Among the specific weather conditions, temperature and precipitation play an important role in the abundance of the mosquito population. When the temperature begins to rise in the spring, mosquito activity begins, and peaks as the temperature continues to rise through the summer, and gradually declines as fall approaches (Hess et al., 1963). Warmer weather conditions are known to shorten both the time intervals between blood meals and the larval development period (Hartley et al., 2012; Ciota et al., 2014). In addition, the longevity of the mosquitoes is influenced by temperature. The Illinois WNV vectors thrive at temperatures that range from 15 to 30 degree Celsius (Andreadis et al., 2014). While warmer temperatures will generally result in more mosquitoes, when the temperature is higher than 30 degree Celsius, the mortality of adult *Culex* vector mosquitoes increases (Andreadis et al., 2014), thereby complicating the role of temperature in the mosquito life cycle. Further, higher temperatures enhance the replication rate of the virus in the mosquitoes making them infectious more quickly (Dohm et al., 2002; Reisen et al., 2006; Kilpatrick et al., 2008; Ruiz et al., 2010). The ongoing changes in the global climate, with a projected rise in the global mean temperature between 1.4 and 5.8°C by the end of this century (Patz et al., 2005), will have an impact in the expansion of mosquitoes into new areas, and thereby may increase the probability of WNV and other mosquito-borne diseases invasion into these areas (Morin and Comrie, 2013; Paz, 2015).

Precipitation is another important weather component that is directly related to the mosquito life cycle. The *Culex* vector mosquitoes require wet conditions to lay their eggs, and rainfall is crucial in maintaining these breeding sites (Jones et al., 2012). However, heavy rainfall might wash away the mosquito larvae, thereby decreasing the mosquito population (Gardner et al., 2012). Several studies have shown that higher mosquito abundance is observed in the areas that are proximate to natural standing water incuding ponds and wetlands (Leblond et al., 2007; Valiakos et al., 2014). Mosquito abundance is also influenced by other conditions such as the availability of mosquito predators, such as mosquito-larvae feeding fish species, dragonflies, and other aquatic zooplanktons (Chase and Shulman, 2009). Intermittent drought conditions can lead to a reduction in these predator populations (Chase and Knight, 2003). In the absence of natural predators, there would be more mosquitoes the next season when rain is again abundant (Chase and Knight, 2003). In addition to natural standing water, there are additional sources of water for mosquito breeding in the form of catch basins, water retention pools, and other artificial water holding structures such as various types of containers and used tires. Catch basins are the structure built in to manage urban run-off but these have been exploited by the mosquitoes, such as *Cx pipiens* as a breeding habitat (Geery and Holub, 1989; Harbison et al., 2014). When there is a decline in the availability of surface water, or outside temperature is very high, water retained in catch basins provide an excellent breeding ground for the *Cx.* vector mosquitoes (Kronenwetter-Koepel et al., 2005; Gardner et al., 2013). The availability and the distribution of the catch basins would thus have an impact on mosquito population in an area.

In addition to weather conditions, the local landscape and land use patterns have an impact on the dynamics of local mosquito populations. The availability of mosquito breeding areas is determined by the structure and water holding capability of the soil in that landscape (Boelee et al., 2013). Further, vegetation and trees provide nectar for feeding, as well as resting sites for adult mosquitoes (Grimstad and DeFoliart, 1974; Burkett-Cadena et al., 2008). The detritus from the vegetation can affect water chemistry and attract or repel ovipositing female mosquitoes (Gardner et al., 2013). In the case of WNV transmission, vegetation also plays a role by attracting bird population thereby increasing the chances of vector-host interaction (Cody, 1981). Several previous studies have attempted to examine the relationship between landscape variables and mosquito population dynamics, with the results indicating differences observed in these associations. This may be due to the local adaptation of the mosquito populations as well as to the measurement of vegetation at varying spatial scales (Diuk-Wasser et al., 2006; Brown et al., 2008a; Chuang et al., 2012; Landau and van Leeuwen, 2012; Gardner et al., 2013). Urbanization and changing land-use patterns have also been linked with an increase in the mosquito population, and mosquito-borne diseases (Gubler, 2011; Li et al., 2014).

Various surveillance systems have been developed by public health agencies to monitor and estimate the risk of human exposure from pathogens transmitted by mosquitoes. For WNV, surveillance methods include mosquito and dead bird collection and testing, monitoring of sentinel birds, and using reported human or horse cases as a spatial and temporal indicator of risk (Control and Prevention, 2000). The ultimate goal of these surveillance systems is to reduce illness through targeted mosquito control, to reduce the number of infected vector mosquitoes and for effective educational messages to warn citizens to reduce individual exposure.

1.2. RATIONALE AND SCOPE

One important problem with current surveillance is that the locations of cases of WNV human illness are not always strongly correlated with other indicators of WNV presence. In particular, the areas and times with higher mosquito infection rates are not always the areas with a higher number of human cases. The reasons for this discrepancy may be related to underreporting of human illness, may be a function of differences in mosquito abundance, or may occur because the virus remains in the sylvatic cycle and does not spill over to humans. In addition, the variable behavior of people may affect their exposure to mosquitoes and these behaviors will vary by income, education level, age and other factors that are clustered in space.

With more than a decade of West Nile virus human and mosquito infection history in Illinois, there has been a tremendous amount of surveillance and research conducted by public health agencies and researchers from both entomological and epidemiological perspectives. For example, the Illinois Department of Public Health holds a data on reported cases of WNV human illnesses and has developed a data repository on the WNV mosquito testing results across Illinois. In addition, mosquito abundance estimates and infection data from a study region in south Cook County, Illinois, an area of ongoing WNV transmission, were collected from 2005 to 2012 by a research team from the University of Illinois, University of Wisconsin, Emory University and Michigan State University. These surveillance and research activities have created a wealth of data, which can be combined with publicly available local weather and landscape data to develop a prediction model for West Nile virus risk estimation. However, there might be some biases associated with these data. Human illness data result from a form of passive surveillance inherent in the reportable disease system of the U.S. It relies on cases to be reported by physicians and it represents only those people who both sought medical care and were tested for WNV. Thus, they do not represent the true WNV infection status in humans, which was estimated to be 3 million infections and 780,000 symptomatic illnesses from 1999-2010, compared to 12,823 reported cases during the same time period (Petersen et al., 2013b). In the Illinois statewide mosquito surveillance data, the compilation of mosquito testing surveillance activities were conducted by different municipalities and mosquito abatement districts across Illinois, and thus were collected with some variability in the techniques employed. This might have an effect on the consistency of the data.

Data on weather conditions help to explain some of the variability of the risk of illness from WNV at the national level, but these conditions vary by region, and it is difficult to determine precise processes at the local level. There are two published approaches to weather-based WNV predictive modeling in Illinois. One is based on mosquito infection and focuses on northeastern Illinois (Ruiz et al., 2010, Shand et al. 2016), and the other is based on mosquito species dynamics for Champaign County (Kunkel et al., 2006). However, such models are lacking at the state level across the latitudinal gradient found in the state of Illinois. Development of a generalizable predictive model of mosquito infection rate based on weather conditions in Illinois would help fill that gap. Such predictive models based on historical data will be helpful for public health agencies to prepare themselves for future WNV outbreaks and allocate the resources where and when the risks are highest. This dissertation will refine, verify, and expand the existing statistical models of WNV mosquito infection using the weather as a key factor.

The local abundance of *Culex* mosquitoes is critically important for the West Nile virus transmission cycle and is influenced by the local weather as well as other environmental and landscape features. However, very few studies have been conducted to understand the joint effects of both weather and landscape conditions on vector mosquito abundance. To add to the complexity, the trapping methods used to capture the mosquitoes might influence the mosquito abundance measures. This dissertation will help to develop a model of vector mosquito abundance using local weather conditions and landscape features. In addition, the effect of trapping methods on mosquito abundance measures will be evaluated.

Finally, in the Chicago, Illinois region, human WNV illness has been consistently reported since 2002. However, there remains a gap in knowledge in our understanding of the fine-scale drivers of spatiotemporal variation in human WNV illness in that area. Particularly, there is an incongruity in the areas with high mosquito infection and human illness in some years but not in others. With more data available now for both human illness and mosquito infection, we are in a better position to evaluate the fine scale drivers of the spatiotemporal variability of human illness. We will use long-term data on local weather, land cover, socioeconomic conditions, and mosquito infection to improve our understanding of the fine-scale drivers of human WNV illness.

1.3. OBJECTIVES

It is evident that the risk of exposure to mosquito-borne pathogens is complicated by the transmission cycle of the pathogen, the dynamic nature of conditions that affect mosquito abundance and species- and regionally-specific mosquito biting behavior. The overall objective of this dissertation is to improve our understanding of the spatial and temporal variability of risk for transmission of WNV to humans through a critical examination of the factors hypothesized to affect exposure to WNV infected mosquitoes by using new approaches to assess exposure risk (Figure 1.1). As it is morphologically difficult to differentiate *Culex pipiens* complex and *Culex restuans* mosquitoes (Harrington and Poulson, 2008), and these two groups of *Culex* mosquitoes (Hamer et al., 2008a) are the main vector of WNV in Illinois, *Culex pipiens* complex and *Culex restuans,* are considered together in this analysis. Hereafter, they will be simply referred as *Culex* mosquitoes. The specific objectives of this dissertation are as follows:

i. Determine the relationship between *Culex* mosquito abundance, the urban landscape, and seasonal and other environmental features in suburban, Chicago, Illinois: If there are more *Culex* mosquitoes, both birds and people are more likely to be bitten by those mosquitoes. This objective will help to improve our understanding of how local mosquito abundance is affected by urban landscape features in the context of dynamic weather events and variability of temperature and rainfall. The main questions addressed for this objective are: (1) How is *Culex* mosquito abundance affected by local weather and by landscape factors? (2) How do different trapping methods affect estimates of *Culex* abundance, and how are these estimates influenced by local weather and landscape?

ii. Determine the simultaneous effects of local weather, urban landscape and other environmental factors on *Culex* mosquito abundance in suburban, Chicago, Illinois: In real life situations, local weather conditions and landscape factors will have combined effects in the mosquito population in an area. This objective will help to improve our understanding of the role of local weather and landscape factors when both of them are considered together in the stastical model. The main questions addressed for this objective are: (1) What are the combined effects of local weather and landscape factors on the *Culex* abundance? (2) Does this relationship vary depending upon the mosquito trapping methods?

iii. Analyze the relationship between weather and WNV mosquito infection rates across a latitudinal gradient in Illinois and develop weekly predictive models to improve local West Nile virus risk response for public health and vector control: Infected mosquitoes are a prerequisite for humans to be exposed to WNV, but the relationship between increased mosquito infection rates and the local risk of human illnesses is not the same across different landscapes. In this objective, predictive models of the WNV mosquito infection rate will be developed using prior weather conditions for the state of Illinois and nine different climate divisions in Illinois. Long-term data available through the Illinois Department of Public Health and publicly available weather data will be used to develop the prediction model. This objective will assess the degree to which limited mosquito testing can be used to provide robust estimates of the risk of WNV. Finally, guidelines will be developed to suggest how the estimates from the models can be used to provide improved public health messages about the future risk for WNV.

iv. Assess the fine-scale dynamic effects of weather, land cover, mosquito infection and socioeconomic conditions to understand the drivers of West Nile virus human illness: This objective will reveal the fine-scale dynamic drivers of West Nile virus illness in humans in the Chicago region. This objective will improve our understanding of the degree to which the mosquito infection rate is a good representation of the spatial and temporal variability of WNV human cases in Illinois. The overall goal of this objective is to improve the understanding of spatial and temporal variability of risk for transmission of WNV to humans and to identify the characteristics of areas where human illness may be under-reported, or where infection in mosquitoes fails to spill over into people.

1.4. FIGURES

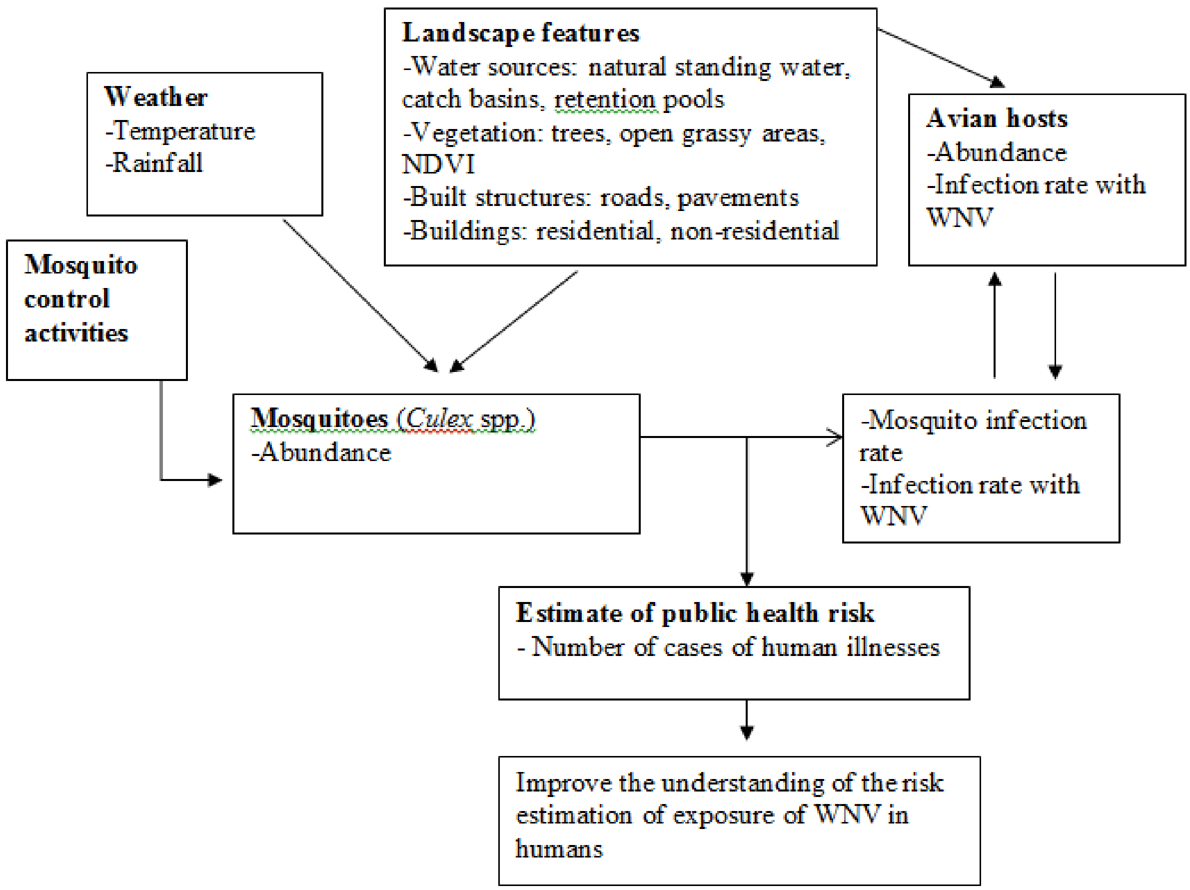

Figure 1.1. Schematic diagram showing the factors that affect public health risk of West Nile virus and that can be assessed to improve the understanding of the risk estimation of WNV in humans.

CHAPTER 2: EFFECT OF TRAPPING METHODS, WEATHER, AND LANDSCAPE ON ESTIMATES OF *CULEX* VECTOR MOSQUITO ABUNDANCE

2.1. ABSTRACT

The local abundance of *Culex* mosquitoes is a central factor in the risk of West Nile virus (WNV) transmission, and vector abundance data influence public health decisions. This study evaluated differences in abundance estimates from mosquitoes trapped using two common methods: CO_2-baited CDC light traps and infusion-baited gravid traps in suburban, Chicago, Illinois. On a weekly basis, the two methods were modestly correlated (r=0.219) across 71 weeks over four years. Lagged weather conditions of past few weeks were found to be associated with the collections in light and gravid traps. Collections in light traps were higher with higher temperature in the same week, higher precipitation one, two and four weeks before the week of trapping, and lower maximum average wind speed. Collections in gravid traps were higher with higher temperature in the same week and one week earlier, lower temperature four weeks earlier, and with higher precipitation two and four weeks earlier. *Culex* abundance estimates from light traps was significantly higher in semi-natural areas compared to residential areas, but abundance estimates from gravid traps did not vary by landscape type. These results highlight the importance of surveillance method in the assessment of local *Culex* abundance estimates. Measures of risk of exposure to WNV should assess carefully how mosquito abundance have been estimated and integrated into assessments of transmission risk. [1]

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2.2. INTRODUCTION

The World Health Organization has estimated that vector-borne diseases account for nearly 17% of the global burden of all infectious diseases (WHO, 2015). Mosquitoes are one of the most important disease vectors and can transmit many pathogens resulting in diseases including malaria, dengue, West Nile disease, St. Louis encephalitis, yellow fever, Japanese encephalitis, Zika and chikungunya (Weaver and Reisen, 2010). The risk of exposure to mosquito-borne illness is often estimated using indices that include vector abundance. Vectorial capacity, for example, takes into account the vector, host, and vector-host interaction, and is a commonly used risk index for malaria and dengue (Garrett-Jones and Shidrawi, 1969; Anderson and Rico-Hesse, 2006; Ceccato et al., 2012). Similarly, dengue transmission risk is often measured using the house index, which is the percentage of houses infested with larva or pupae of *Aedes* mosquitoes (Scott and Morrison, 2003).

Estimates of interactions between vectors and hosts are also commonly used to estimate West Nile virus (WNV) transmission risk (Ciota et al., 2013). Due to the multi-host transmission cycle of WNV, Kilpatrick et al. developed an index combining vector abundance, the fraction of blood meals taken from mammals, WNV infection prevalence and a vector competence index for alternative vector species to assess WNV transmission risk (Kilpatrick et al., 2005). A simpler vector index, measured as the product of mosquito abundance and the WNV infection rate in mosquitoes, has also been used for WNV transmission risk estimation (Gujral et al., 2007; Bolling et al., 2009; Kilpatrick and Pape, 2013). The advantage of the later method is simple to calculate, however it does not take into account the vector competence. Because mosquitoes of different species transmit different pathogens, vector-pathogen-host interactions differ across systems. As a result, system-specific abundance and infection risk estimates must be tailored for particular mosquito-borne diseases and particular areas (Reisen, 2010).

In the United States, mosquitoes of the genus *Culex* are the vectors for WNV transmission, with nearly 96% of the WNV positive pools obtained from just a few *Culex* species (Andreadis, 2012). The proportional distribution of these species varied by region, with *Cx. tarsalis*, *Cx. quinquefasciatus* and *Cx. pipiens pipiens and Cx.restuans* being dominant in the western, southern, and north central regions, respectively (Andreadis, 2012). In the Chicago, Illinois, region, which is the focus of this study, *Cx. pipiens* complex and *Cx. restuans* have played the most important role in enzootic as well as the epidemic cycle of West Nile virus transmission (Hamer et al., 2008a). In Chicago area, *Cx. pipiens* form molestus has been detected rarely (Mutebi and Savage, 2009). The life history of *Culex* mosquitoes includes aquatic stages (eggs, larvae, and pupae) and the adult terrestrial stage. Females lay rafts of eggs on the surface of the water, with a preference for water rich in organic content. Depending upon weather and food availability, adults emerge in about 10-14 days (Crans, 2004). Adult gravid female *Cx. pipiens* enter diapause in the fall to overwinter (Vinogradova, 2000; Crans, 2004).

Temperature and precipitation play an important role in the life history and population dynamics of mosquitoes. In temperate climates, warmer weather in the spring accelerates mosquito activity, and higher temperatures generally shorten the time between bloodmeal acquisition and oviposition (Reisen, 2010; Hartley et al., 2012). The lifespan of adult *Culex spp.* varies considerably depending on the temperature. Adult female mosquitoes raised over a range constant temperatures had an average longevity ranging from 11 days to over 92 days (Lebl et al., 2013; Andreadis et al., 2014; Ciota et al., 2014). The shortest observed life span for both sexes was less than two weeks at 30 $^{\circ}$C, while they survived more than 90 days at 15 $^{\circ}$C

(Andreadis et al., 2014). This indicates that mosquito population will be higher when the tempertaure is between 15- 30 °C, while it will be lower when the temperature exceeds 30°C. In natural systems, weather conditions in the weeks prior to mosquito capture ("lagged weather") can predict mosquito abundance (DeGaetano, 2005; Walsh et al., 2008; Carrieri et al., 2014) and even off-season meteorological conditions can affect mosquito abundance due to diapause conditions (Chase and Knight, 2003) and predator dynamics as increased mosquito population were observed following the drought (Cailly et al., 2011).

Many other factors can affect local abundance of mosquitoes. For example, the availability and distribution of larval habitats depends on both weather and local landscape features. Suitable larval habitats, such as natural water bodies, catch basins and containers, are required to maintain the mosquito population in an area (Jones et al., 2012) and rainfall plays a key role in maintaining these habitats. *Culex* mosquitoes need wet conditions to reproduce, but heavy rainfall can reduce the survival rate of *Culex* vectors both at the adult stage and during larval development (Gardner et al., 2012; Gardner et al., 2013). Local vegetation influences mosquito abundance by providing resting sites and sugars to mosquitoes, and different species of vegetation can promote or reduce the emergence rates of adult *Culex* mosquitoes (Brown et al., 2008a; Gardner et al., 2015). In urban areas of Connecticut, significantly higher numbers of *Cx. pipiens* and *Cx. restuans* were found in areas with moderate vegetation as measured from imagery using a vegetation index (Crowder et al., 2013). In other studies, orchard habitat (Chuang et al., 2012), forested areas (Landau and van Leeuwen, 2012) and medium height trees were associated with higher *Culex* abundance (Trawinski and Mackay, 2010). In a study conducted in Amherst, Erie County, NY, *Culex* abundance increased with more mixed urban land use, grass and agriculture land cover, and industrial and recreational areas (Reisen and Pfuntner, 1987).

The abundance of *Culex* spp. mosquitoes in an area is estimated by counting the number of *Culex* spp. mosquitoes collected per trap and then adjusting that for the number of nights in which traps were actually set. The most commonly used traps to collect *Culex* mosquitoes are dry ice baited CDC light traps and infusion-baited gravid traps. Dry ice baited light traps attract mosquitoes by releasing CO2, whereas gravid traps attract ovipositing mosquitoes by providing breeding habitat. Light traps attract host-seeking female mosquitoes that may be unfed and nulliparous or parous (DiMENNA et al., 2006) and are useful to capture a diversity of mosquito species (Moore et al., 1993) whereas gravid traps primarily collect ovipositing female *Culex* mosquitoes (Williams and Gingrich, 2007). Mosquitoes collected in gravid traps are especially suitable for WNV surveillance if detection of infection status is included in the surveillance plan, because gravid mosquitoes have had at least one gonotropic cycle and are thus more likely to be infected (Hribar et al., 2003; Krebs et al., 2014). Underlying weather conditions and trap locations might affect the number of *Culex* being captured in light and gravid traps; however, the differences in these relationships are not well documented.

The main objective of this study was to compare abundance measures and factors associated with differences between two common methods for trapping *Culex* vectors in Illinois: CDC light traps baited with dry ice and gravid traps containing a liquid oviposition attractant. We evaluated the effects of trapping method on estimates of *Culex* abundance, taking into account weekly weather and landscape features. We conducted the study between 2009 and 2012 in a suburban Chicago, Illinois, a region with significant WNV activity. Secondarily, we evaluated the relationship between *Culex* abundance and WNV mosquito infection rate during the same period.

2.3. MATERIALS AND METHODS

Study area and data sources

The study area was in south Cook County, Illinois, located in the near suburbs of the city of Chicago (Figure 2.1). The area is approximately 17 km^2 with a population of around 20,000 people in several municipalities. This study was part of a broader investigation of WNV transmission ecology (Hamer et al., 2008b; Hamer et al., 2014).

Mosquitoes were collected for 18 weeks from late May to early October each year (weeks 22 to 39) from 2009 to 2011 and for 17 weeks (weeks 23 to 39) in 2012, using both CDC miniature light traps and infusion-baited gravid traps. Light traps were hung from a tree or other structure at a height of about 1.5 meters above the ground with a cooler containing dry ice attached each night. Gravid trap oviposition attractant was made by placing a half cup of alfalfa pellets in five gallons of water into a carboy that had been placed in the sun for about seven days prior to use (to allow fermentation of organic matter) and changed every two to four weeks. The traps were set up in the evening, and collected the next morning during each week of collection. Traps were distributed throughout the study area in different representative landscapes, including semi-natural sites (cemeteries, parks, and rights of way), and residential areas. The basis of the site selection has been described elsewhere (Hamer et al., 2008a; Hamer et al., 2008b; Hamer et al., 2009; Hamer et al., 2014). Over the four-year study period, the number of light trap locations ranged from 29 to 76 per year, with 119 unique locations; and the number of gravid trap locations ranged from 11 to 31 per year, with 48 unique gravid trap locations. The unique traps were located at least 50m away from each other and a maximum of 3,649m for light traps and 3,799m for the gravid traps. Some, but not all, of the trap locations were used in all four years. Among the 119 and 48 unique light and gravid trap locations, 53 light and 29 gravid traps were located in semi-natural areas, whereas 66 light and 19 gravid traps were in urban residential areas.

After collection, mosquitoes were identified by species and sex, and then pools of up to 50 female *Culex* spp. (*Cx. pipiens* complex and *Cx. restuans*) were tested for WNV using quantitative rt-PCR (Harrigan et al., 2014). Given the difficulties inherent in morphologically differentiating *Cx. pipiens* complex and *Cx. restuans*, these two species were pooled together and hereafter would be referred to as *Culex* spp. (Hamer et al., 2009). The identification of the mosquito species was done by the trained and experienced personnel in the field. *Culex spp.* are considered the primary enzootic and bridge vectors of WNV in this area (Hamer et al., 2009; Andreadis, 2012). The average number of *Culex* spp. per trap night was calculated for each trap location and for the 71 collection weeks across 2009 to 2012. The minimum infection rate (MIR) of WNV in mosquitoes was estimated using the maximum likelihood method implemented in the program PooledInfRate version 4.0 (CDC, 2006). In addition to calculating the MIR for the field-collected mosquito collections, we obtained and calculated the MIR of *Culex* spp. from WNV testing reported to the Illinois Department of Public Health for Cook County during the same time period.

Daily weather records from January 2009 to December 2012 were obtained from the nearest NOAA weather station at the Midway International Airport, Chicago, Illinois, 9 miles north of the study area. Weather records included daily minimum and maximum temperature, precipitation, average humidity, and average and maximum wind speed. Average weekly temperature (˚C) was calculated as the mean of the minimum and the maximum temperature for each week.. Weekly average daily humidity, average wind speed and maximum windspeed were calculated as the mean of their respective seven readings from that week, and weekly precipitation was calculated as the sum of the precipitation during that week.

Statistical analysis

The weekly abundance estimates from light trap collections were compared with the abundance measures from gravid traps. Then, temporal and spatial analyses were performed separately for light and gravid traps. The response variable for all analyses was the average number of *Culex* per trap night. Data from traps where a trap failed on a given night were removed from analyses, to avoid the artifact of pseudo-negative catches. In total, 802 and 222 data points were removed from light traps and gravid traps respectively for this reason. Predictor variables for temporal analyses included weekly average temperature, weekly total precipitation, average humidity, average wind speed, average maximum wind speed of the same week. In addition, we included each of these predictor variables with one to four week lags. In total, there were 25 weather variables: five each for temperature, precipitation, average humidity, average wind speed and average maximum wind speed (Table 2.1).

Descriptive statistics were calculated using the command PROC UNIVARIATE in SAS 9.4 (SAS Institute Inc., Cary, NC, USA). The Shapiro-Wilk W statistic (>0.9) was used to test normality of outcome variables. In the original dataset, the *Culex* spp. per trap night in both light and gravid traps were not normally distributed (W<0.9). We subsequently identified *Culex* spp. per trap night data above the 95th percentile, and pools having higher than that value were assigned the value of the 95th percentile; after which data were normally distributed (W>0.9). Pearson's product-moment correlation coefficient was used to measure the association between average *Culex* spp. per trap night by trap type. Bivariate correlation analyses of individual predictor variables were conducted, and variables with $p < 0.2$ were selected for inclusion in a multivariable regression model. Multiple linear regression analysis was performed to explore the relationship between the response variable and the selected predictor variables using the command PROC GLM in SAS. The variance inflation criterion (VIF<10) was used to evaluate multicollinearity among explanatory variables. The Akaike Information Criterion (AIC) was used to evaluate candidate models. The model with the lowest AIC value was selected as the model that best fit the data (Akaike, 1974). The variable selection criterion for the final multivariate regression was $p < 0.05$.

For spatial analysis, light and gravid trap locations from 2009 to 2012 were classified as being either in residential areas or in semi-natural areas. Analysis of variance (ANOVA) tests were performed to evaluate whether *Culex* spp. abundance in light and gravid traps differed by land cover type. The dependent variable was the average number of *Culex* spp. per trap night in gravid traps and light traps. The independent variable was landscape type (whether the traps were located in residential or semi-natural areas).

2.4. RESULTS

Light traps captured 18,978 *Culex* spp. mosquitoes from 3,444 trap nights with 14 to 76 light traps set per week during 71 weeks from 2009 to 2012. Across all light trap collections, abundance estimates ranged from 0 to 266 *Culex* spp. per trap night, with an overall mean of 5.5 (±12.9 SD). Weekly light trap collections combined for all sites averaged between 0.4 to 24.3 *Culex* spp. per trap night, with a mean of 5.1 (±3.9 SD). Annually, for light traps, the highest overall average *Culex* spp. per trap night was in 2010, with a value of 7.2 (±5.5 SD). The next highest average abundance estimates per trap night was 4.5 (±3.1 SD) in 2009, followed by 4.4 (±3.4 SD) in 2012, and 4.1 (±2.8 SD) in 2011.

Gravid traps captured a total of 22,345 *Culex* spp. from 1,561 trap nights with 6 to 31 gravid traps set per week during the same period. Across all gravid trap collections, abundance estimates ranged from 0 to 533 *Culex* spp. per trap night with a mean of 14.3 (±33.2 SD). Weekly gravid trap collections combined for all sites averaged from 0.1 to 192.6 *Culex* spp. per trap night with a mean of 16.1 (±24.6 SD). For gravid traps, the highest overall average *Culex* per trap night was in 2009, with a value of 26.2 (±44.5 SD). The next highest average abundance estimates per trap night was 18.6 (±13.1 SD) in 2010, followed by 10.1 (±9.1 SD) in 2012, and 8.4 (±7.0 SD) in 2011. The highest annual MIR for the small study area alone was 15.7 in 2009, followed by 11.8 in 2010, 9.2 in 2012 and 0.6 in 2011. County-level MIR was 1.0 in 2009, 5.3 in 2010, 9.8 in 2012, and 3.5 in 2011.

Gravid traps usually captured more *Culex* spp. than light traps (Figure 2.2). The exception was during the weeks 35 to 39 in 2011 and weeks 36 to 38 in 2012, when the light traps had higher capture rates. This may be a random event as weather conditions during those weeks were within the normal range. The weekly *Culex spp.* abundance estimates (Figure 2.3) averaged across the four years demonstrated that there was greater variance in *Culex* spp. abundance collected in gravid traps compared to light traps, and there was a slight peak in gravid trap collections around weeks 26-29 and again at weeks 32-34. In light traps, a bimodal distribution was observed with a first peak at week 26 and a second peek at weeks 32 to 34 (Figure 2.3). After week 33, abundance was generally low and decreasing in both trap types, and most of the anomalous *Culex* spp. collections occurred earlier in the season.

With 71 weeks of data without truncating for outliers, there was no measurable correlation between average abundance in light traps and the average abundance in gravid traps (r=0.03). However, after truncating the outliers, the correlation was stronger, although still marginal (r=0.219; p=0.06; N=71) (Figure 2.4).

Temporal analysis

Using AIC criterion, light trap data were best fit with a model that included five weather variables (AIC = 319.6), which explained 28% of the variation in *Culex* spp. abundance (adjusted R^2 = 0.276) (Table 2.2). For gravid traps, data were best fit with an analogous model including five weather variables (AIC = 484.2), which explained about 30% of the variability of abundance (adjusted R^2 = 0.303) (Table 2.3). In light traps, the *Culex* spp. abundance was higher with higher temperature in the same week, higher precipitation one, two and four weeks before, and a lower maximum average wind speed in the same week (Table 2.4). In gravid traps, the *Culex* spp. abundance was higher with higher temperature in the same week and one week before, higher precipitation two and four weeks before, and lower temperature four weeks before (Table 2.5).

Spatial analysis

Of the 119 light trap collections, 53 were in semi-natural areas and 66 were in residential areas. From the light traps, the average number of *Culex* spp. captured in natural areas was 5.3 (±5.0 SD) and was 2.7 (±3.1 SD) in residential areas. Of the 48 gravid trap locations, 29 were in semi-natural areas and 19 were in residential areas. From gravid traps, the average number of *Culex* spp. captured in natural areas was 12.4 (±8.5 SD) whereas for residential areas it was 11.8 (±7.5 SD). While both light and gravid trap collections resulted in higher numbers of *Culex* spp.

when traps were located in the semi-natural areas (Figure 2.5), the difference was statistically significant only for light traps ($p = 0.0002$).

2.5. DISCUSSION

Our results demonstrated that *Culex* abundance estimates across urban landscapes vary with trapping method, and that spatial, temporal, and weather-related factors influence these estimates. In particular, strong winds reduced abundance in light traps, but did not affect gravid trap collections. Abundance was generally higher in semi-natural areas from both trap types, but this difference was stronger for light traps. Both gravid and light traps had higher abundance when set during weeks with warmer temperatures and when conditions were wetter during the prior several weeks. Higher abundance in gravid traps also followed warmer temperatures during the prior week, but this effect was not seen in light traps. Cooler temperatures four weeks prior also increased gravid trap abundance.

Gravid traps collected more *Culex* spp. mosquitoes compared to light traps. The differences observed in the collections from light and gravid traps may be related to their ability to collect mosquitoes in different life stages.

Temperature is an important predictor of mosquito abundance because it affects life history traits of mosquitoes. The positive association between prior temperature and *Culex* abundance has been observed in several other studies (Pecoraro et al., 2007; Paz and Albersheim, 2008; Jacob et al., 2009; Wang et al., 2011; Lebl et al., 2013; Mulatti et al., 2014). Mechanistically, high temperatures may support faster growth of mosquito larvae (Hagstrum and Workman, 1971), adult emergence and subsequent capture. However, following emergence, the ambient temperature may either increase or decrease adult mosquito longevity. Lebl et al (2013) found that higher temperatures two weeks prior to capture increased *Culex* abundance in light traps (Lebl et al., 2013) where accumulated temperature one to four weeks before capture was negatively correlated with *Culex pipiens* abundance (Roiz et al., 2014). These equivocal findings suggest that there may be a temperature threshold, above or below which mosquito survival and activity markedly decrease. Higher abundance of mosquitoes in gravid traps after cooler temperatures four weeks before suggests that mosquito longevity may increase in cooler temperatures (Mordecai et al., 2013).

Precipitation also appears to drive *Culex* abundance. The positive relationship between precipitation at one to four weeks prior and *Culex* abundance has also been observed in other studies (Hamer et al., 2009; Lebl et al., 2013; Hamer et al., 2014). However, the relationship between precipitation and *Culex* abundance is not necessarily linear. Pecoraro et al. (2007) found no association between weekly precipitation and *Culex* abundance (Pecoraro et al., 2007), but at more protracted temporal scales, correlations were positive in some years and negative in others (Jacob et al., 2009). Lebl et al. (2013) found that precipitation had a weaker association with abundance than other weather variables, with higher precipitation over 10 weeks associated with higher abundance. In our Chicago study system, Gardner et al. (2012) documented that *Culex* larval abundance was associated with low rainfall, suggesting that precipitation greater than 3.5 cm during a single week may “flush” immature *Culex* out of larval habitat (Gardner et al., 2012). Our data with adult mosquitoes demonstrates a similar pattern, where precipitation in weeks prior to sampling predicts adult abundance by providing habitat for adult females to lay egg rafts. Alternatively, this relationship between high *Culex* abundance following rain events might have more to do with more conducive ambient conditions for adults (e.g. higher humidity reducing desiccation risk), which could promote activity and increase trapping success. Though the gravid traps can themselves act as a larval habitat because of the water availability in those traps, we found positive relationships between the prior rainfall (two and four weeks earlier) and *Culex* spp. abundance estimates in both light and gravid traps.

Wind speed affects mosquito host-seeking activities and flight direction. In this study, maximum average wind speed of the same week of capture was negatively associated with *Culex* abundance in light traps but not gravid traps. The reason for this difference may be associated with trap placement. CDC light traps were set approximately 1.5 m above the ground, whereas gravid traps were placed directly on the ground: it is possible that this subtle difference in trap height may have exposed host-seeking and adult females to different wind conditions (Darbro and Harrington, 2006). Indeed, Hamer et al. (2014) found that *Culex* spp. may move as far as 2.48 km, and that this dispersal was likely facilitated by wind (Hamer et al., 2014). Similarly, Lebl et al (2013) found that average wind speed three weeks prior to capture was negatively associated with *Culex* abundance (Lebl et al., 2013).

Landscape features may also affect mosquito production through variation in breeding habitat and resting places for adult mosquitoes. We found that in light traps, more *Culex spp.* were captured in natural areas than residential areas, whereas in the gravid traps, this variability was lower. Availability of hosts and competition with natural container habitats, respectively, may modify these relationships. For example, more birds in natural areas could result in more host-seeking mosquitoes being available for light trap capture. Lower numbers of *Culex* mosquitoes light traps in residential areas may also be related to mosquito abatement practices that target those areas, such as pesticide aerial treatments for adult mosquitoes and the placement of larvicides in urban catch basins (Harbison et al., 2014). In a study conducted in Suffolk County, New York, the highest abundance of *Cx. pipiens* was in areas where WNV was mostly prevalent in birds, not in humans, and this may be the case in the current study region as well (Rochlin et al., 2009). Further, comparison of our findings to other studies is somewhat confounded by how landscapes are defined. Our study occurred within an urban area, and our semi-natural areas were relatively small patches within a highly urbanized landscape. If we had used the same index urbanization that was used to assess *Culex* abundance in New York, all our sites would have been classified as “urban” (Drummond et al., 2006).

The estimated abundance of mosquitoes was not clearly correlated with negative public health outcomes. The Illinois Department of Public Health reported only one human WNV case in Cook County Illinois in 2009 when abundance estimates from gravid traps were higher than any of the four years. There were 30 cases in 2010, 22 cases in 2011 and 174 cases in 2012, clearly indicating that 2012 was a WNV outbreak year (IDPH, 2015). In this year, the temperature was above average (hot) and rainfall was below average (dry), supporting prior patterns of higher MIR observed by Ruiz et al (Ruiz et al., 2010). The MIR was also higher in 2012 in Cook County at large, but the local MIR in 2012 in our smaller study area was higher in 2009 and 2010 than in 2012, highlighting the variability of the WNV transmission at different scales. Messina et al. (2011) found that MIR in the Chicago area was not associated spatially with human illness after controlling for other factors in a multivariate regression, and differences in mosquito abundance or a failure to capture temporal and spatial dynamics may have accounted for this (Messina et al., 2011). It was not possible to compare the relationship between mosquito abundance, MIR and the reported WNV human illness at a broader level, due to the lack of comprehensive mosquito abundance data at that scale. Future work should assess additional abundance measures and alternative spatio-temporal approaches.

Mosquito vector abundance is an important theoretical predictor of human infection, especially for multi-host pathogens. However, the weak correlation between the mosquito abundance estimates and human WNV illnesses observed in our study area may be related to the geographic scale of operation. Our data demonstrate that in the Cook County, Illinois, gravid and light traps set at the same time in similar conditions do not produce identical abundance estimates. Rather, temperature and precipitation of the capture week and one to four weeks earlier played important roles in the temporal variation of *Culex* abundance in both light and gravid traps, but other relationships were not the same for both trap types. Maximum average wind speed in the same week was negatively associated with *Culex* abundance in light traps but not in gravid traps. Spatially, higher numbers of *Culex* mosquitoes were captured from semi-natural areas compared to residential areas in the light traps, but not in the gravid traps. These findings highlight both the importance of local weather and landscape features in combination with the trapping methods for the development of mosquito abundance measures that are relevant to public health. The findings indicate that abundance estimates obtained from only one type of trap may not truly represent the underlying mosquito abundance, and a combination of trapping methods might give a better picture.

2.6. FIGURES AND TABLES

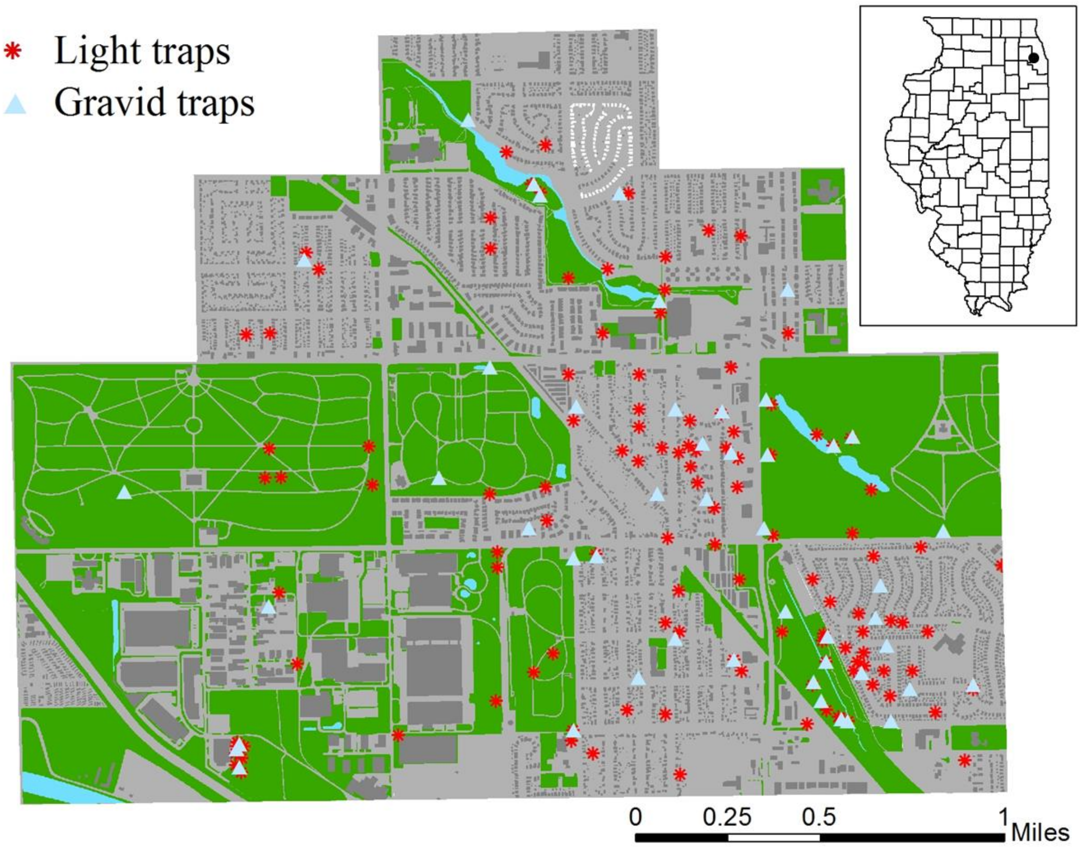

Figure 2.1. Light and gravid trap sampling locations in suburban Chicago. Stars represent CDC light traps, solid triangles represent gravid traps. Green color indicates semi-natural areas, whereas gray color indicates urban residential or commercial areas. The inset shows the state of Illinois, USA with the black dot indicating the neighborhoods where mosquito collections occurred (Alsip, Evergreen Park, Oak Lawn) between 2009 and 2012.

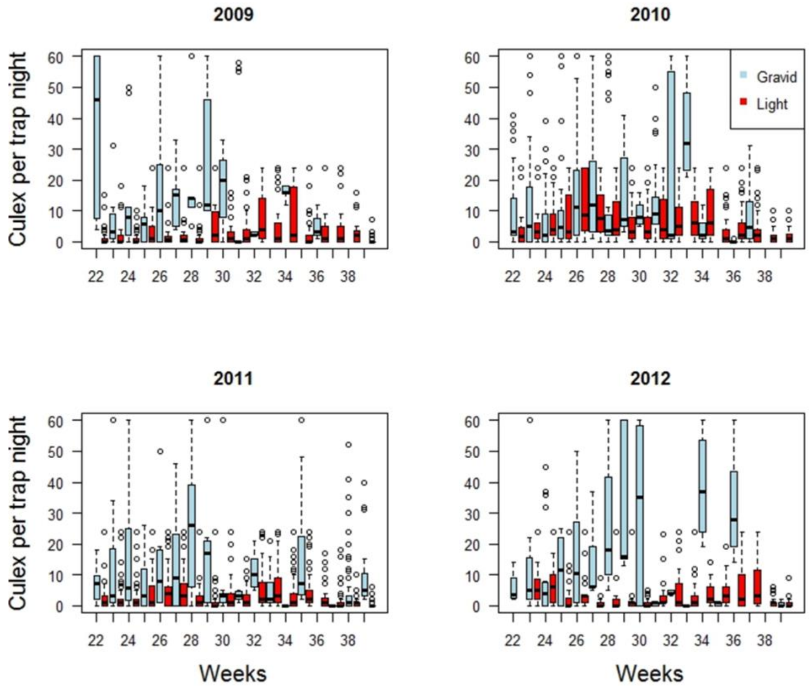

Figure 2.2. Box plots of the weekly average *Culex* abundance in light and gravid traps from 2009 to 2012.

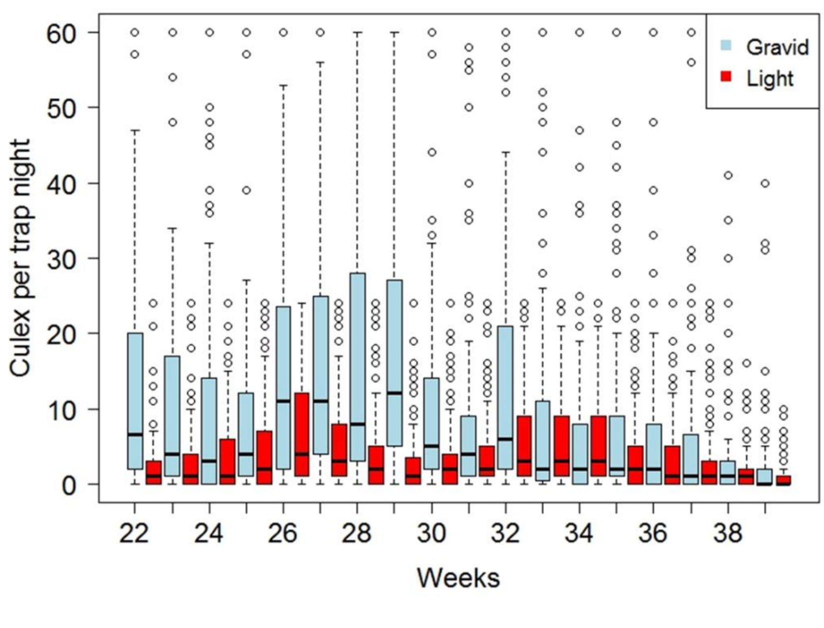

Figure 2.3. Box plot of overall weekly *Culex* abundance in light and gravid traps with weeks combined for the years from 2009 to 2012.

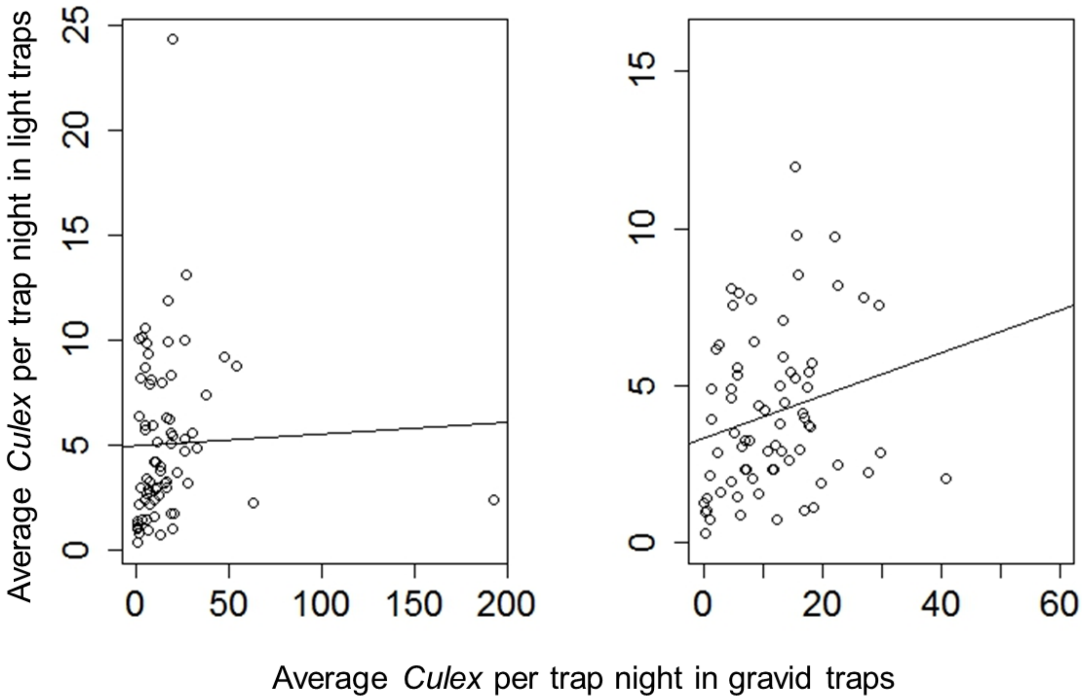

Figure 2.4. Scatter plots between weekly average *Culex* per trap night in light and gravid collections with all original numbers (left) and after truncating of outliers (right).

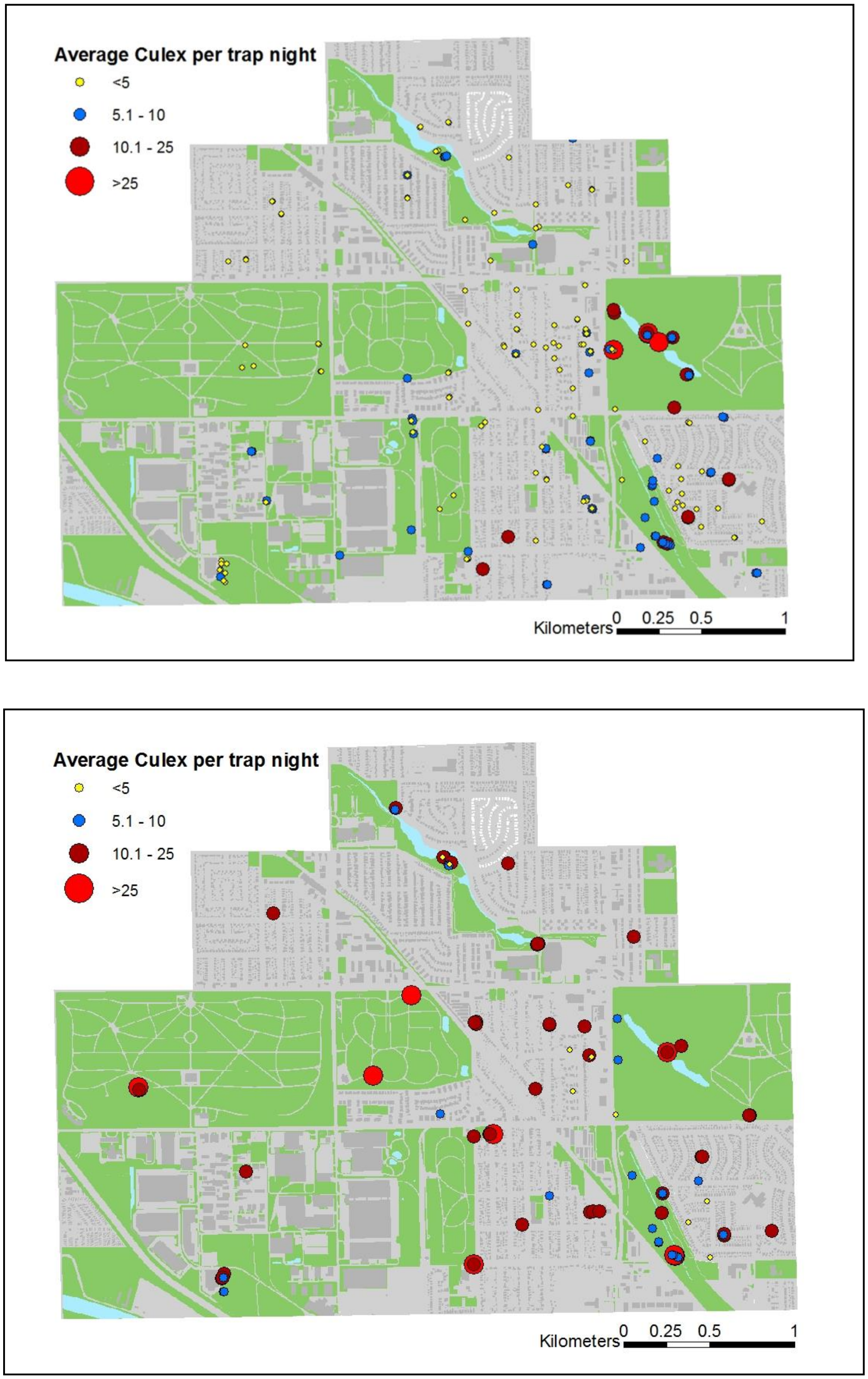

Figure 2.5. Map showing the spatial distribution of *Culex* per trap night in light (top) and gravid collections (bottom).

Table 2.1. List of explanatory variables used in the temporal analysis to show their relationship with weekly *Culex* abundance in light and gravid traps.

S.N.	Variables	Abbreviation
A	Temperature (Degree Celsius)	
1	Average temperature of the same week	Temp_samewk
2	Average temperature one to four weeks before	Templagwk1, Templagwk2, Templagwk3, Templagwk4,
B	Precipitation (Centimeters)	
1	Average precipitation of the same week	Preci_samewk
2	Average precipitation one to four weeks before	Precilagwk1, Precilagwk2, Precilagwk3, Precilagwk4
C	Humidity (Percentage)	
1	Average humidity of the same week	Avghumidity_samewk
2	Average humidity one to four weeks before	Humiditylagwk1, Humiditylagwk2, Humiditylagwk3, Humiditylagwk4
D	Average wind speed (Kilometer per hour)	
1	Average wind speed of the same week	Avgwind_samewk
2	Average wind speed one to four weeks before	Avgwindlagwk1, Avgwindlagwk2, Avgwindlagwk3, Avgwindlagwk4
E	Average maximum wind speed (Kilometer per hour)	
1	Average maximum wind speed of the same week	Avgmaxwind_samewk
2	Average maximum wind speed one to four weeks before	Avgmaxwindlagwk1, Avgmaxwindlagwk2, Avgmaxwindlagwk3, Avgmaxwindlagwk4

Table 2.2. Candidate models for predicting the abundance of *Culex* spp. abundance collected in light traps.

Model	Variables included	K	-2 Log likelihood	AIC	ΔAIC
1	Avgtemp_samewk, Precilagwk1-2 and 4, Avgmaxwind_samewk	6	305.6	319.6	0
2	Avgtemp_samewk, Templagwk1, Precilagwk1-2 and 4, Avgmaxwind_samewk	7	304.2	320.2	0.6
3	Avgtemp_samewk, Precilagwk1 and 4, Avgmaxwind_samewk	5	309	321.0	1.4
4	Avgtemp_samewk, Templagwk1, Precilagwk1-4, Avgmaxwind_samewk	8	303.4	321.4	1.8
5	Avgtemp_samewk, Templagwk1, Precilagwk1-4, Avgwindlagwk3, Avgmaxwind_samewk	9	302.5	322.5	2.9
6	Avgtemp_samewk, Templagwk1, Precilagwk1-4, Humiditylagwk2, Avgwindlagwk3, Avgmaxwind_samewk	10	302.2	324.2	4.6
7	Avgtemp_samewk, Templagwk1-2, Precilagwk1-4, Humiditylagwk2, Avgwindlagwk3, Avgmaxwind_samewk	11	302.2	326.2	6.6
8	Null model	1	333.8	337.8	18.2
9	Global (all explanatory variables included)	26	285.1	339.1	19.5

Table 2.3. Candidate models for predicting the abundance of *Culex* spp. abundance collected in gravid traps.

Model	Variables included	K	-2 Log likelihood	AIC	ΔAIC
1	Avgtemp_samewk, Templagwk1 and 4, Precilagwk2 and 4	6	470.2	484.2	0
2	Avgtemp_samewk, Templagwk1 and 4, Precilagwk4	5	472.5	484.5	0.3
3	Avgtemp_samewk, Templagwk1 and 4, Precilagwk2 and 4, Avgwindlagwk4	7	470.2	486.2	2.0
4	Global (all explanatory variables included)	26	448.9	502.9	18.7
5	Null	1	501.2	505.2	21.0

Table 2.4. Model parameters for the top ranked model using weather variables to predict the abundance of *Culex* spp. in light traps.

Variable	Parameter estimate	F-value	P-value	Standardized parameter estimate
Average temperature of the same week	0.219	3.04	0.003	0.332
Precipitation one week before	0.212	2.13	0.036	0.229
Precipitation two weeks before	0.183	1.80	0.076	0.199
Precipitation four weeks before	0.216	2.22	0.029	0.232
Maximum average wind speed of the same week	-0.117	-1.92	0.058	-0.217

Table 2.5. Model parameters for the top ranked model using weather variables to predict the abundance of *Culex* spp. in gravid traps.

Variable	Parameter estimate	F-value	P-value	Standardized parameter estimate
Average temperature of the same week	0.515	1.79	0.077	0.240
Temperature one week before	0.746	2.25	0.028	0.313
Temperature four weeks before	-0.721	-3.59	0.0006	-0.387
Precipitation two weeks before	0.437	1.44	0.153	0.146
Precipitation four weeks before	0.665	2.21	0.031	0.221

CHAPTER 3: SIMULTANEOUS EFFECTS OF WEATHER AND LANDSCAPE ON THE ESTIMATES OF CULEX ABUNDANCE IN SUBURBAN CHICAGO, ILLINOIS

3.1. ABSTRACT

The abundance of certain *Culex* mosquitoes is critically important for the West Nile virus transmission cycle and weather, landscape, and other environmental features influence this abundance. Such influences are not uniform and vary among regions. In the past, only a few studies have evaluated the combined effects of these different components on *Culex* abundance. In this study, our main objective was to evaluate the simultaneous effects of weather, landscape and other environmental features on *Culex* abundance within a region with significant WNV activity in suburban, Chicago, Illinois for the period from 2009 to 2012. Our main questions in this study were: (1) How do weather, landscape, and other environmental features simultaneously affect *Culex* mosquito abundance, and (2) how does this vary between mosquitoes captured in light traps compared to gravid traps? A multi-level modeling approach was used to measure these relationships. We found that weather variables were the primary drivers of the variation in the *Culex* abundance measures but some local landscape features were also important. Further, we confirmed that the associations we observe differ depending upon the trapping methods used to capture the mosquitoes. The measures of abundance from gravid and light traps were different; highlighting the need to assess more carefully measures of mosquito abundance on disease risk measures that estimate vector density. The findings of this study highlight the importance of dynamic weather and landscape features for *Culex* mosquito abundance.

3.2. INTRODUCTION

Mosquito-borne diseases, including malaria, dengue, Zika, yellow fever, West Nile virus (WNV), and chikungunya, are a significant contributor to the global disease burden (WHO, 2014). The distribution and intensity of these different diseases are not uniform across the globe and vary depending upon the availability of vector mosquitoes, disease agents, climate, public health infrastructure and socioeconomic conditions (Reisen, 2010; Haley, 2012; Kilpatrick and Randolph, 2012). In the U.S., WNV is the leading cause of mosquito-borne illness since its first introduction in 1999 in New York (Krow-Lucal, 2017). WNV is transmitted primarily by mosquitoes of *Culex* species, as more than 96% of the WNV positive pools in the U.S. were recorded from a relatively few species (Andreadis, 2012). In the Chicago, Illinois, region, which is our study site, the two species *Cx. pipiens* and *Cx. restuans*, are the primary bridge vectors for WNV transmission (Hamer et al., 2008a).

The presence of vector mosquitoes in an area is a prerequisite for the local transmission of mosquito-borne diseases. Vector mosquito abundance determines the relative number of mosquitoes of particular species in an area during the time of sampling and can be an important indicator to evaluate both risk of illness and the effectiveness of mosquito control efforts (Nasci et al., 2013). Though higher numbers of mosquitoes in an area does not always indicate higher risk for mosquito-borne diseases, in a study conducted in Maricopa County, Arizona in 2010, higher number of *Culex quinquefasciatus* mosquitoes were found in WNV outbreak areas (22.2 *Cx. quinquefasciatus* per trap night) compared to the control sites (8.9 *Cx. quinquefasciatus* per trap night) (Godsey Jr et al., 2012; Colborn et al., 2013). In general, the combination of mosquito abundance and infection status determines the risk of mosquito-borne diseases in a particular area. Mosquito abundance is an important component of commonly used vector indices to estimate the WNV risks in humans. These are calculated as an integration of WNV infection rate and vector abundance (Gujral et al., 2007; Kilpatrick and Pape, 2013). The mosquito abundance, in turn, is influenced by local weather conditions, landscape structure, environmental features, demographic characteristics and mosquito abatement practices (Brown et al., 2008a; Trawinski and Mackay, 2008; Ruiz et al., 2010; Buckner et al., 2011; Chaves et al., 2011; Deichmeister and Telang, 2011; Chen et al., 2013).

Among various weather conditions, temperature, precipitation, humidity and wind speed affect the mosquito population either by altering their life cycle stages or flight behavior. Mosquito activity begins as temperature increases in the spring. The warmer temperature shortens the gonotrophic cycle of mosquitoes and developmental rate of mosquito larvae, thereby leading to higher numbers of mosquitoes per gravid female (Hartley et al., 2012; Beck-Johnson et al., 2013). Higher temperatures are also known to increase the WNV infection rate in mosquitoes due to enhanced viral replication (Kilpatrick et al., 2008). However, the survivability of the adult mosquito is decreased when the temperature increases above 30 degree Celsius (Andreadis et al., 2014; Ciota et al., 2014). Precipitation is crucial to determine the availability of breeding sites for the mosquitoes. Stagnant water is required for *Culex* mosquitoes to breed, and rainfall in prior weeks creates such breeding pools for the mosquitoes (Reisen et al., 2008). However, the intensity and heterogeneity of the rainfall patterns differentially affect mosquito abundance (Valdez et al., 2017). For example, heavy rainfall washes out the larvae and pupae thereby negatively affecting the adult mosquito emergence rate (Gardner et al., 2012; Jones et al., 2012). Other weather parameters such as relative humidity and wind speed affect the mosquito abundance by influencing their flight activities and oviposition dynamics (Chaves and Kitron, 2011; Lebl et al., 2013).

Apart from the weather, the local landscape structure and changes in land use patterns affect vector mosquito abundance (Ferraguti et al., 2016; Zittra et al., 2017). The availability and distribution of water sources, vegetation, grasslands, and built structures in a landscape determines the availability of mosquito breeding habitats and resting sites for mosquitoes (Brown et al., 2008a; Trawinski and Mackay, 2010; Chuang et al., 2012; Crowder et al., 2013). In addition, the topographic characteristics and soil type of the local landscape affect the water-holding capacity and maintenance of water puddles after a rainfall (Yokoo et al., 2008). Another important environmental feature that influences mosquito abundance in urban areas are catch basins, structures built to manage the urban runoff. *Culex* mosquitoes breed in these basins especially during the hot dry seasons when surface water sources are less available (Crans, 2004; Gardner et al., 2013; Harbison et al., 2014). Additionally, the landscape characteristics surrounding the catch basins determine the suitability of the catch basins for mosquito breeding. In the Chicago area, higher number of *Culex* larvae were found in the catch basins located near the curbside and had three or more deciduous trees within 20 m distance, while lower numbers of *Culex* larvae were found in the catch basins with a higher proportion of impervious surface within 10m distance of the basins (Harbison et al., 2017).

The reported associations between landscape features and *Culex* abundance differs among studies. This may be due to differences in mosquito populations in different regions as well as the use of different spatial scales. For example, in a Connecticut study, 10 different buffer sizes ranging from 100m to 1 km radius around the trap location, at an increasing order of 100m were used to assess the impact of landscape variables on mosquito abundance (Diuk-Wasser et al., 2006). They found that *Culex pipiens* abundance was negatively associated with forested areas, with the strongest associations observed in 400m buffer. In a study conducted in

Henrico County, Virginia, a 400m buffer was used where stormwater structures were strongly associated with *Culex* abundance (Deichmeister and Telang, 2011). In Tucson, Arizona, five different buffers from 10m to 50m around the trap location were used and found that medium height trees and pavement were positively and shrubs were negatively associated with *Culex* abundance with 30m buffer having the strongest associations (Landau and van Leeuwen, 2012).

We understand that several studies have evaluated the effects of weather and landscape features on the estimates of *Culex* abundance (Pecoraro et al., 2007; Brown et al., 2008b; Barker et al., 2009; Buckner et al., 2011; Chaves et al., 2011; Deichmeister and Telang, 2011; Roiz et al., 2014; Roiz et al., 2015; Karki et al., 2016; Zittra et al., 2017). However, most of these studies focused on only one of these components and failed to capture the combined and simultaneous effects on the estimates of *Culex* abundance. In real-world scenarios, both weather and landscape simultaneously affect the mosquito abundance in a local area.

A few studies have taken into account both weather and landscape features together to model the estimates of *Culex* abundance (Chaves et al., 2011; Rosà et al., 2014; Yoo, 2014; Yoo et al., 2016). These spatiotemporal models are different from one another in terms of methodologies used, variable selection, and the temporal and spatial scales of study. For example, Chaves et al (2011) used a regression tree analysis in a dataset from 2005- 08 in the Chicago region using summer temperature and precipitation, and a landscape variable based on the Shannon diversity index to evaluate the mosquito diversity and abundance, and found that increased temperature and more diverse communities were associated with lower abundance *Culex pipiens* mosquitoes. In a study in northwestern Italy using 11 years of data from 2001- 11, Rosa et al (2014) used a linear mixed model approach using weather factors (weekly mean temperature, growing degree weeks using 9° C as baseline, weekly total precipitation and number of rainy days), and landscape variables (NDVI), normalized difference water index (NDWI), and nearest distance from trap site to urban center and rice fields. From this analysis, they determined that the spatiotemporal patterns of *Culex pipiens* abundance were affect by the weather early in the year together with local land-use. Likewise, Yoo et al (2014) used three different Poisson generalized linear models to analyze the weekly *Culex pipiens-restuans* abundance in 2007-08 using weekly temperature and precipitation of one week before, proportion of water body within a radius of 0.2 km from each trap, normalized difference vegetation index (NDVI) within 1 km radius, and human population density as the covariates. They showed that site-specific random effects Poisson generalized linear mixed model was the best model for their data, and found that weekly average temperature and NDVI was positively, and human population density negatively associated with the *Culex pipiens-restuans* abundance (Yoo, 2014). They further extended this study by including data of more years (2005- 08) and more covariates that included weekly weather conditions up to 5 weeks earlier, and four environmental variables: water surface, built-up area, open area and vegetation area within a 1 km buffer from the trap site, and elevation. They found that a site-specific random effects model with temporal autocorrelation was the best model, and harmonic temperature, precipitation, vegetation and built areas were positively and elevation negatively associated with *Culex pipiens* abundance (Yoo et al., 2016).

In our earlier analysis, we evaluated the effects of weather and of landscape separately in the same study area of suburban, Chicago, Illinois from 2009 to 2012, a region with significant WNV activity (Karki et al., 2016). In this study, our main objective was to extend that analysis and evaluate the relationship between *Culex* abundance with the weather, landscape, and other environmental features simultaneously. In our earlier study, landscape was characterised as either natural or residential but in this study, we included six different landscape categories and other environmental features such as the presence of catch basins and tree density. Our main questions in this study were: (1) What are the landscape characteristics surrounding the traps with records of high and low mosquito captures on average? (2) What is the joint effect of local weather, landscape and environmental features in *Culex* mosquito abundance in an urban environment? and (3) Do the trap methods used to capture mosquitoes affect these relationships?

3.3. MATERIALS AND METHODS

Study area and mosquito data

Our study area is located in the suburban region of Chicago, Illinois in south Cook County (Figure 3.1). More than 20,000 people live in this area comprised of different municipalities. It has an area of about 17 km^2. We chose this area due to the availability of rich longitudinal data sources as this region was a part of the broader investigation into the WNV eco-epidemiology due to the persistent presence of WNV in Chicago area (Chaves et al., 2011; Hamer et al., 2014; Krebs et al., 2014; Karki et al., 2016). Mosquitoes were collected each summer from late May to early October using a combination of light and gravid traps from the years 2005 to 2012. In this analysis, only data from 2009 to 2012 were used due to the availability of more uniform data. The number of light and gravid traps ranged from 29 to 76 and 11 to 31 respectively. The trap locations were distributed to represent all major local microhabitats in residential areas, cemeteries, parks, locations near to natural water and wooded areas. The details on the collection procedures, trap distribution, and site selection has been described elsewhere (Hamer et al., 2014; Krebs et al., 2014; Karki et al., 2016). After collection, trained field staff identified and counted *Culex* mosquitoes. In this analysis, both *Culex pipiens* and *Culex restuans* were counted together as they are the bridge vectors for WNV transmission in Chicago area (Hamer et al., 2008a), and they are morphologically difficult to differentiate in the field (Kilpatrick et al., 2005).

Landscape and environmental variables

We developed a detailed groundcover map of the study area from high-resolution aerial photography obtained from the National Agriculture Imagery Program. The landscape features were classified into six different groups defined as ***buildings*** (residential and non-residential buildings), **open *grasslands*** (open grassy areas, recreational facilities, and other open natural areas), ***lawns*** *(included driveways and walkways)*, ***natural water*** (natural bodies of water and retention basins), ***wooded***, and ***manmade cover*** (roads and larger parking lots) (Figure 3.2).

We used the spatial pattern analysis software, FRAGSTATS version 4.2 (McGarigal, 2012) to quantify the landscape features within a 100m buffer measured from each trap location. We chose the 100m size both as a good representation of much of the *Culex* mosquitoes range while avoiding a large overlap of buffers. In FRAGSTATS, our input layer was a 1m*1m resolution raster grid of the study area that represented the eight land types described above. We used the 8 cell neighborhood rules and partial sampling strategy. We calculated the proportion of each landscape feature within each buffer and the connectance index of each of the landscape features. The connectance index is a measure of functional joining between patches of the corresponding patch type, where each pair of patches is either connected or not. It varies from zero to 100, where zero indicates none of the focal classes are connected and 100 indicate every patch of the focal class is connected (McGarigal, 2012).

We calculated the normalized difference vegetation index (NDVI) to estimate the amount and condition of vegetation present using the USDA National Agriculture Imagery Program

(NAIP) for the years 2010, 2011 and 2012. For the 2009 analysis, we used the imagery of 2010 as the NAIP imagery was not available for 2009. NDVI was calculated from the near infrared and visible red bands of the images using the formula: NDVI = (NIR- Red) / (NIR + Red), where NIR= near infrared. The values of NDVI vary from -1 to +1, where low values (<0.1) indicate barren areas, moderate values (0.2- 0.3) indicate shrub and grassland and high values (0.6- 0.8) indicate areas with high vegetation and forests (Jagai et al., 2007).

The locations of 3,443 catch basins in the study area were obtained by GPS field survey conducted in 2013. We calculated the number of catch basins present within a 100m radius from each trap and calculated the nearest distance of a catch basin from each of the traps. In addition, we calculated the nearest distance to natural water from each of the traps using ArcGIS 10.1.

The species and locations of trees were obtained from an intensive survey conducted in 2009. In residential areas, the survey sampled every fifth residential lot, where the number, size, and species, genus, or family of observable trees was recorded within each lot. In non-residential areas, a 50m grid was imposed and then 20% of the grids were selected randomly for data collection. For the current analysis, we used spatial interpolation with data for each of the 1,219 sampling points to estimate the distribution of several tree types across the study area. For this analysis, we focused on trees that were in the family *Rosaceae*, (hereafter called “rose family”), maple trees (genus *Acer*) and coniferous trees. These three types of trees were selected because they were relatively common in our study area and earlier work suggested their possible importance relative to mosquito abundance.

Weather variables

The daily weather records from January 2009 to December 2012 on temperature, precipitation, wind speed, and relative humidity were obtained from the nearest NOAA weather station located at the Midway International Airport, about nine miles away from the study site. The daily weather records were converted into weekly summaries. For temperature, relative humidity, and average wind speed, weekly averages were calculated by averaging the 7-day daily recordings for that week. For precipitation, the weekly total was calculated by summing up the total precipitation during the 7 days of that week.

Statistical analysis

For our analysis, we first characterized the micro level landscape surrounding the traps that exhibited high, medium and low numbers of mosquitoes per trap night. We did this for light and gravid traps separately based on their distribution pattern. The traps were classified as high, medium and low if the average number of *Culex* mosquitoes captured were greater than 5, 1 - 5, and less than 1 per trap night in light traps and greater than 15, 10 - 15, and less than 10 per trap night in gravid traps.

We used a multilevel modeling approach to analyze the number of mosquitoes per trap night weekly. Weather variables varied temporally whereas the landscape variables were considered static but varied spatially across the trap locations. The trap locations were treated as random effects in the model. Our outcome variable was the number of *Culex* per trap night in gravid traps and in light traps. Our explanatory variables included four broad categories of weather parameters: temperature, precipitation, wind speed and relative humidity and three broad categories of landscape: vegetation, built environment and urban water features (Table 3.1). Log transformation of mosquito data have often been used as a response variable in similar studies but this transformation can leads to biased estimates or inaccurate confidence intervals (O'hara and Kotze, 2010; Yoo, 2014). Poisson models are most commonly used methods to model the count data. However, in mosquito data where values of zero are common, it is difficult to meet the assumptions of equality of means and variances required by the Poisson models. To overcome this issue, alternate two-parts models such as zero-inflated Poisson (ZIP), zero-inflated negative binomial (ZINB), Poisson hurdle (PH) and Negative binomial hurdle (NBH) are available (Voronca et al., 2014; Park et al., 2015). We chose Negative binomial hurdle (NBH) model as our model of choice as Akaike information criteria (AIC) value was lowest for this model compared to other models. The negative binomial hurdle model is a two-part model, where the first part is a binary logit model (presence/ absence) and the second part handles the positive counts only (Park et al., 2015). For each part of the model, first bivariate analyses of the individual variables were conducted with the outcome variable. Variables with $P<0.2$ were selected for inclusion in the multivariate model. Stepwise multiple linear regression analysis was performed to explore the relationship between the outcome variable and explanatory variables. The level of significance used in the final multivariate regression was $P<0.05$. The statistical analysis was conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

3.4. RESULTS

Descriptive statistics

Trapping intensity varied across the years. The number of light traps set out across one year ranged from 29 to 76 while the number of gravid traps ranged from 11 to 31 (Table 3.2). The number of *Culex* mosquitoes per trap night captured in light trap collections was highest in 2010 (8.25) followed by 2012 (4.54), 2009 (4.43) and 2011 (4.24) (Table 3.2). In gravid trap collections, more mosquitoes per trap night were collected in 2009 (26.58) followed by 2010 (18.64), 2012 (10.45) and 2011 (8.16) (Table 3.2). The weekly weather conditions varied across the years; with 2010 experiencing a lot of rainfall while the year 2012 was hot and dry (Table 3.3, Figure 3.3).

Landscape characteristics

Both light and gravid traps that captured a higher number of *Culex* mosquitoes on average were closer to the natural water sources, and away from the catch basins (Table 3.4). The other landscape characteristics that were associated with the capture of a higher number of *Culex* mosquitoes in the light traps included higher proportions of the 100 m buffer area made up of natural water, open grasslands and wooded areas. In addition, lower proportions of buildings, lawn areas, rose family trees, and fewer numbers of catch basins around 100m buffer were observed near traps with higher *Culex* capture (Table 3.4). In the gravid traps, the landscape characteristics surrounding high capturing traps were a higher proportion of open grasslands, and lower proportions of lawn, wooded areas, and maple trees (Table 3.4). There was no clear pattern in the distribution of the proportion of buildings, average ndvi, and coniferous trees surrounding the high, medium and low *Culex* capturing traps in both the light and gravid traps.

Regression analysis

Our multi-level analysis for the light trap collections indicated that temperature, humidity and wind speed were associated with the presence of *Culex* mosquitoes while also controlling for spatial factors (Table 3.5). The binary model indicated that average temperature of one and three weeks before was negatively but temperature four weeks before was positively associated with *Culex* presence (Table 3.5). Likewise, relative humidity two weeks before was positively and three weeks before was negatively associated with *Culex* presence. Average wind speed one to three weeks before was negatively associated with *Culex* presence. Among variables related to landscape, *Culex* presence was positively associated with the nearest distance to catch basins but was negatively associated with the number of catch basins within 100m buffer from the trap locations and the nearest distance to natural water sources (Table 3.5).

In the count model for the light traps, we found that average temperature of the same week and an average temperature of two and four weeks before were positively and temperature three weeks before were negatively associated with the number of *Culex* mosquitoes trapped (Table 3.5). Precipitation one week before was positively and two weeks before was negatively associated with the number of *Culex* mosquitoes trapped. Relative humidity two and four weeks before was positively associated with the *Culex* abundance. Average wind speed of the same week and two weeks before was positively and four weeks before negatively associated with the *Culex* abundance (Table 3.5).

For the gravid trap collections, the average temperature of the same week and precipitation four weeks before was positively and relative humidity of one week before was negatively associated with *Culex* presence (Table 3.6). Among the landscape features, the proportion of manmade cover was positively and density of maple trees was negatively associated with the *Culex* presence. In the count model, the average temperature of the same week and one and three weeks before were positively but four weeks before was negatively associated with the *Culex* abundance (Table 3.6). Likewise, precipitation two and four weeks before was positively but three weeks before was negatively associated with the *Culex* abundance. Average wind speed three weeks before was positively associated and average humidity of the same week was negatively associated in the count model. Among the landscape features, maple density and proportion of wooded areas were negatively associated with the *Culex* abundance (Table 3.6).

3.5. DISCUSSION

Mosquito abundance measures are affected by different weather, landscape and environmental features in a local area. In this study, we evaluated the simultaneous effects of microclimatic and landscape structure in the abundance of *Culex pipiens/restuans*, a vector for WNV infection, in a suburban environment of an area from where WNV human cases have been consistently reported. We found that weather variables were mainly driving the variation in the *Culex* abundance measures but some of the local landscape features were also significantly contributing to it. Further, we confirmed our earlier findings – but this time controlling for landscape features while assessing weekly changes in the weather, that the association we observe differ depending upon the trapping methods used to capture the mosquitoes (Karki et al., 2016).

We found that the higher temperature of the same week led to higher numbers of *Culex* mosquitoes in both light and gravid traps. This showed that even when landscape and other environmental features are taken into account, higher temperature drives the mosquito abundance process. This result is in agreement with the previous findings that the temporal variations in the mosquito abundance are driven by higher temperature (Lebl et al., 2013; Karki et al., 2016; Ruybal et al., 2016). The higher abundance during warmer weather is related to a shorter mosquito development period (Abouzied, 2017). The prior weeks' temperature up to four weeks also played an important role in *Culex* abundance but they were not consistently positive indicating that the sequence of warm and cool weather in earlier weeks might be important. Precipitation of earlier weeks also played an important role in processes that affect mosquito abundance but their direction was not consistent, indicating that the events of dry and wet are affecting this process. Other studies have also found that the role of precipitation is not straightforward and *Culex* abundance processes are affected by the number of rainy days and intensity of rainfall (DeGaetano, 2005; Jones et al., 2012; Valdez et al., 2017).

In this study, we observed from the landscape characteristics surrounding the traps affected mosquito abundance. High capture traps included a higher proportion of open grasslands and wooded areas. This is similar to findings by Trawinski and Mackay (2010), who also found a positive association of grass and agricultural land with *Culex* abundance. Traps capturing a higher number of *Culex* mosquitoes were closer to natural water sources and had a higher proportion of natural water sources within a 100m buffer. As water is required for mosquito breeding, we expected to see a higher number of mosquitoes being captured in the traps near to water sources. The finding related to natural water is consistent with other studies that found that the proximity to water sources was positively correlated with the mosquito abundance (Brown et al., 2008b; Rosà et al., 2014; Roiz et al., 2015). However, it was interesting to note that lower numbers of *Culex* mosquitoes were captured near the traps that were closer to the catch basins.

Catch basins are often treated with larvicides to reduce mosquito populations (Rey et al. 2006, Anderson et al. 2011), and though data on catch basin treatments were not available for our use, our discussions with local communities, led us to assume that catch basins were treated. At the same time, the effectiveness of various products, the timing of catch basin treatments, and complications wrought by interactions among factors affecting larval habitats cast doubt on the degree to which this assumption holds (Muturi et al., 2010; Gardner et al., 2012; Harbison et al., 2015).

It is possible that the adult mosquitoes that emerged from catch basins did not stay near them upon emergence. This quick dispersal from the catch basin sites may occur as the immediate surroundings of the basins were not good locations for host seeking or for cover during the daytime. Previous studies showed that land use near the catch basins (Kronenwetter-Koepel et al., 2005; Stockwell et al., 2006) and the design and site locations of the catch basin had an impact on mosquito abundance (Rey et al., 2006). A mark-capture study conducted in South Cook County, Illinois indicated that *Culex pipiens* on average dispersed within 1.15 km from the catch basin they emerged (Hamer et al., 2014). This distance indicates that though catch basins are a good habitat for mosquito development, they will not necessarily within a short distance of them upon emergence. The other possible explanation for a low number of mosquitoes near the catch basins is that the mosquito control efforts in the study region were successful and thus greatly reduced the number of adults that emerge from catch basins (Harbison et al., 2014). If this is the case, then catch basins are protective, because mosquitoes are using them to deposit eggs in large numbers but those eggs are not successful in becoming adults. This would point to the need to administer control to other larval sites besides catch basins since the adult *Culex* population is still large. The lower average distance of natural water bodies from traps was associated with the presence of *Culex* mosquitoes while a higher proportion of water within the 100m buffers was associated with higher *Culex* abundance in light traps but not the gravid traps. This may be due to the fact that the gravid traps act as a breeding habitat and other natural water sources have less effect compared to the light traps.

In conclusion, we determined that in the WNV hotspot of South Cook County, Illinois, weather, vegetation, built environment and urban water features all play important roles in the abundance of *Culex* mosquitoes, with differences observed in the direction of associations and trap types. This indicated that the dynamics of mosquito population are driven by the combined effects of local weather and landscape structure. Most interestingly, fewer *Culex* mosquitoes were found near the catch basins. For further studies, we recommend evaluating the landscape features surrounding the catch basins to evaluate if there are suitable features to support mosquito population or the observance of fewer *Culex* was due to the success of mosquito control activities going on in the area.

3.6. FIGURES AND TABLES

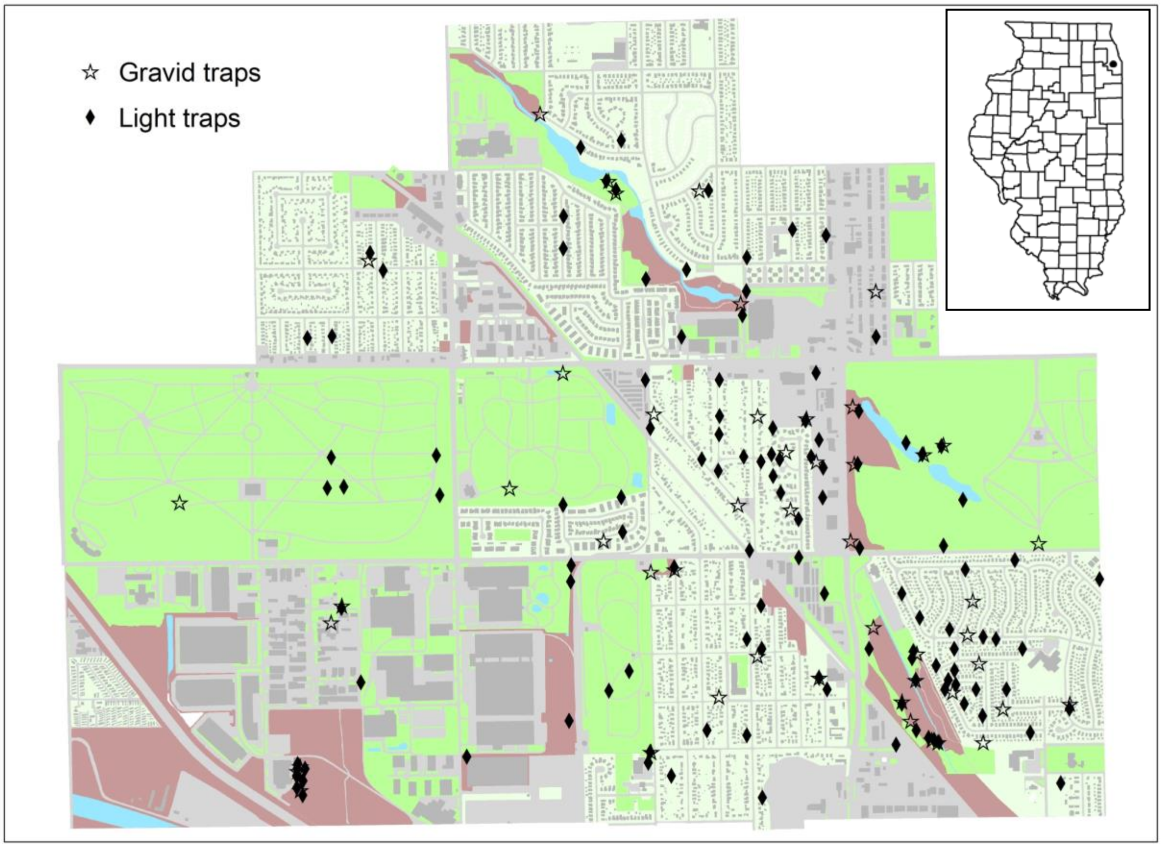

Figure 3.1. Study area showing the distribution of gravid and light trap locations from 2009-2012. The map in the inset shows the state of Illinois with a black dot showing the location of study area.

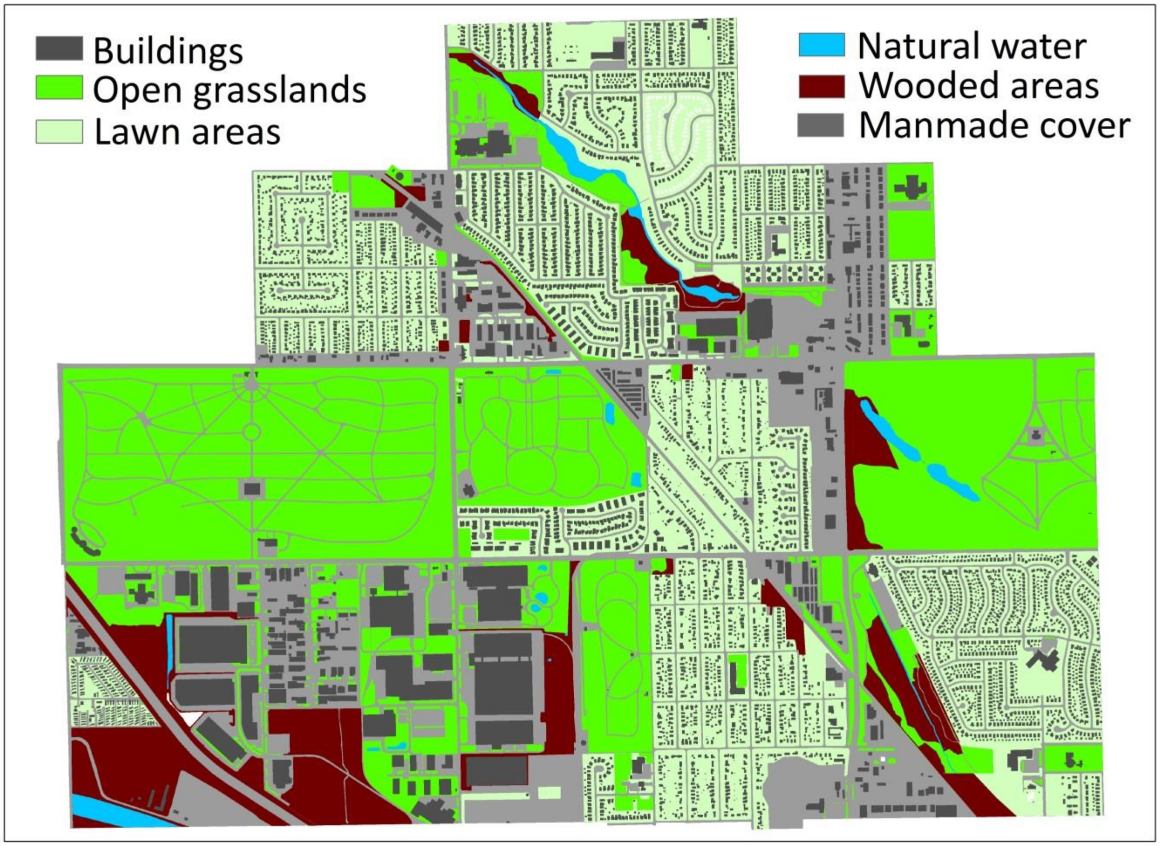

Figure 3.2. Key landscape features of the study region.

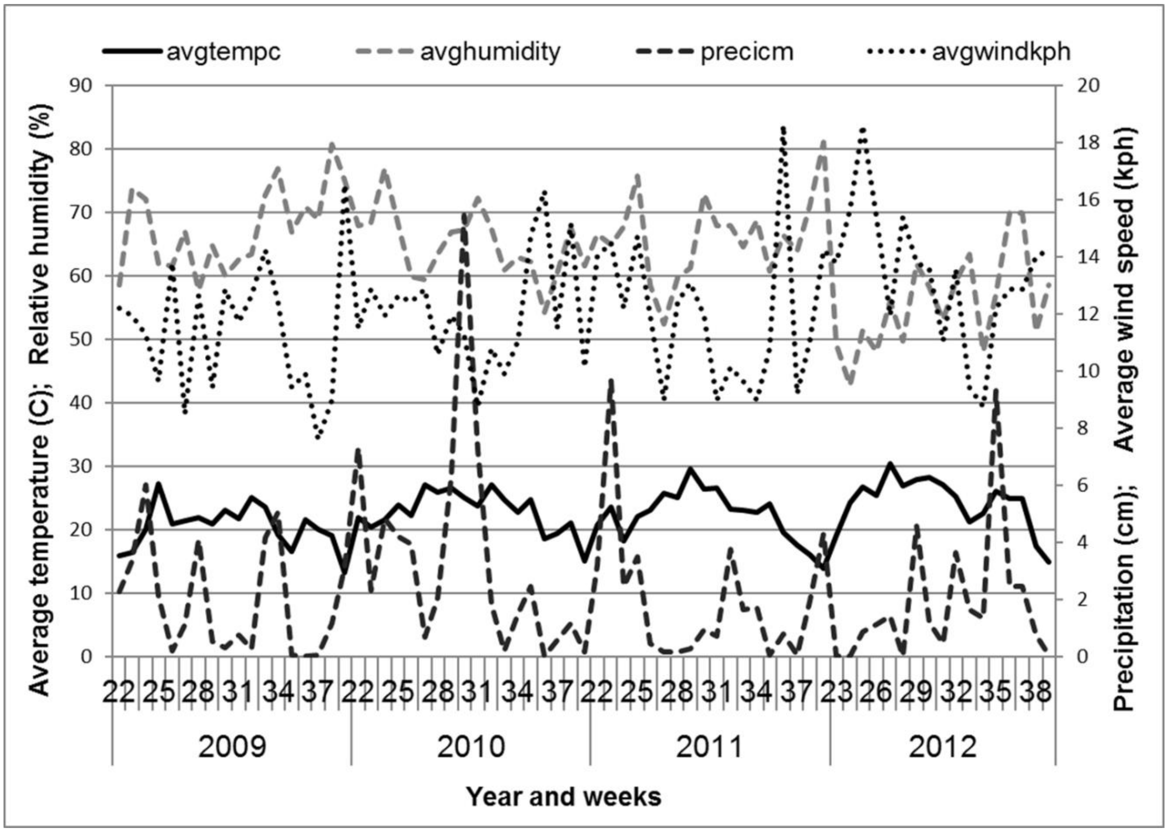

Figure 3.3. Weekly weather (average temperature, total precipitation, average wind speed and relative humidity) conditions during the summer months of 2009- 2012.

Table 3.1. List of explanatory variables.

S.N.	Variables	Notation	S.N.	Variables	Notation
	Landscape			Weather	
A	Vegetation		E	Temperature	
1	Density of coniferous trees	coniden	1	Average temperature of same week	avgtemp
2	Density of rose family trees	roseden	2	Average temperature of one week before	templag1
3	Density of maple trees	mapleden	3	Average temperature of two weeks before	templag2
4	Average NDVI	ndviavg	4	Average temperature of three weeks before	templag3
5	Percentage of lawn cover	pctlawn	5	Average temperature of four weeks before	templag3
6	Percentage of grass area	pctlawn	F	Precipitation	
7	Percentage of wooded areas	pctgrass	1	Average precipitation of same week	avgpreci
8	Connectance index of lawn cover	conlawn	2	Average precipitation of one week before	precilag1
9	Connectance index of grass area	congrass	3	Average precipitation of two weeks before	precilag2
10	Connectance index of wooded areas	conwooded	4	Average precipitation of three weeks before	precilag3
			5	Average precipitation of four weeks before	precilag4
B	Built environment		G	Wind speed	
1	Percentage of manmade cover (streets)	pctmmc	1	Average wind speed of same week	avgwind
2	Percentage of buildings	pctbldg	2	Average wind speed of one week before	windlag1
3	Connectance index of buildings	conbldg	3	Average wind speed of two weeks before	windlag2
			4	Average wind speed of three weeks before	windlag3
C	Urban water features		5	Average wind speed of four weeks before	windlag4
1	Number of catch basins	ncb	H	Humidity	
2	Nearest distance to catch basins	cbdistance	1	Average humidity of same week	avghumidity
3	Percentage of natural water	pctwater	2	Average humidity of one week before	hunidity lag1
4	Nearest distance to natural water	watdistance	3	Average humidity of two weeks before	huniditylag2
			4	Average humidity of three weeks before	humiditylag3
			5	Average humidity of four weeks before	humiditylag4

Table 3.2. Temporal patterns of estimates of *Culex* abundance in light and gravid traps in South suburban Chicago.

Trap type	Year	Number of traps	Number of trap nights	Mean (95% CI)	Minimum	Maximum	Sum
Light traps	2009	35	565	4.43 (12.64)	0	173	2505
	2010	66	771	8.25 (14.51)	0	158	6364
	2011	76	1166	4.24 (12.91)	0	266	4943
	2012	29	412	4.59 (10.8)	0	102	1895
Gravid traps	2009	11	150	26.58 (69.15)	0	533	3987
	2010	27	438	18.64 (34.39)	0	297	8165
	2011	31	503	8.16 (18.56)	0	176	4105
	2012	19	264	10.45 (17.67)	0	108	2759

Table 3.3. Average weekly weather during the summer months from 2009- 2012 in the study area.

	2009	2010	2011	2012
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Temperature (C)	20.42 (3.31)	22.85 (3.14)	22.26 (3.88)	24.26 (3.96)
Precipitation (cm)	1.91 (1.88)	3.45 (3.72)	1.97 (2.30)	1.83 (2.24)
Relative humidity (%)	67.54 (6.53)	64.89 (5.16)	66.24 (6.46)	55.77 (7.42)
Average wind speed (kph)	11.43 (2.23)	12.01 (1.86)	11.96 (2.52)	13.36 (2.29)

Table 3.4. Landscape characteristics around traps in high, medium and low mosquito traps.

Light trap

Variable	High (>5/ trap night)			Medium (1-5/ trap night)			Low =3 (<1/ trap night)		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
watdistance	40	88.1	121.9	55	112.8	128.2	24	150.5	141.8
cbdistance	40	81.7	71.6	55	54.3	39.7	24	27.7	23.4
pctwater	40	3.1	6.6	55	1.3	5.2	24	0.0	0.0
pctwooded	40	17.2	25.9	55	11.1	23.8	24	5.5	13.8
pctgrass	40	24.1	26.4	55	16.7	28.4	24	4.8	16.7
pctmmc	40	19.2	18.7	55	19.7	16.3	24	23.7	20.0
pctbldg	40	10.9	10.6	55	13.1	8.1	24	19.1	6.2
pctlawn	40	25.4	28.5	55	37.8	29.0	24	46.5	24.5
ndviavg	40	0.19	0.08	55	0.13	0.09	24	0.15	0.14
coniden	40	0.00040	0.00060	55	0.00070	0.00063	24	0.00040	0.00050
mapleden	40	0.0006	0.0008	55	0.00082	0.00075	24	0.0003	0.0005
roseden	40	0.00015	0.0002	55	0.00029	0.00029	24	0.0003	0.0004
ncb	40	6.7	7.8	55	8.1	6.6	24	11.4	6.9

Gravid trap

Variable	High (>15/ trap night)			Medium (10-15/ trap night)			Low (<5/ trap night)		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
watdistance	13	47.9	59.5	20	98.9	120.1	15	78.8	74.8
cbdistance	13	75.7	72.0	20	81.6	58.5	15	58.3	50.1
pctwater	13	2.4	6.2	20	1.7	3.1	15	2.6	5.4
pctwooded	13	3.5	8.2	20	20.6	29.0	15	21.8	27.8
pctgrass	13	39.6	33.8	20	14.9	24.7	15	12.5	16.1
pctmmc	13	19.4	15.5	20	18.2	19.9	15	18.9	15.3
pctbldg	13	10.4	8.0	20	12.1	9.5	15	11.5	9.5
pctlawn	13	24.6	25.2	20	32.3	30.5	15	32.6	28.7
ndviavg	13	0.15	0.11	20	0.15	0.14	15	0.13	0.12
coniden	13	0.00075	0.00098	20	0.00083	0.00137	15	0.00056	0.00060
mapleden	13	0.00039	0.00033	20	0.00083	0.00072	15	0.00096	0.00090
roseden	13	0.00023	0.00031	20	0.00024	0.00029	15	0.00035	0.00040
ncb	13	8	6.5	20	5.8	6.9	15	6.9	5.5

Table 3.5. Final multivariate model for light traps.

	Binary Model				Count model				
Variable	Estimate	SE	t-value	P-value		Estimate	SE	t-value	P-value
avgtemplag1	-0.068	0.0289	-2.36	0.0183	avgtempc	0.036	0.0165	2.23	0.0257
avgtemplag3	-0.116	0.0287	-4.06	<.0001	avgtemplag2	0.030	0.0157	1.94	0.0524
avgtemplag4	0.051	0.025	2.08	0.0379	avgtemplag3	-0.036	0.0131	-2.74	0.0062
humiditylag2	0.047	0.0091	5.23	<.0001	avgtemplag4	0.034	0.0164	2.1	0.0357
humiditylag3	-0.023	0.0098	-2.4	0.0165	precilag1	0.055	0.0099	5.55	<.0001
avgwindlag1	-0.058	0.0295	-1.99	0.0462	precilag2	-0.033	0.0102	-3.24	0.0012
avgwindlag2	-0.050	0.0281	-1.81	0.071	humiditylag2	0.027	0.0054	5.09	<.0001
avgwindlag3	-0.098	0.0264	-3.74	0.0002	humiditylag4	0.022	0.0060	3.64	0.0003
cbdistance	0.004	0.0021	2.3	0.0214	avgwindkph	0.043	0.0172	2.53	0.0116
natwatdistance	-0.002	0.0007	-2.98	0.0029	avgwindlag2	0.026	0.0153	1.72	0.0856
ncb	-0.028	0.0164	-1.76	0.079	avgwindlag4	-0.069	0.0154	-4.49	<.0001
					cbdistance	0.005	0.0011	4.42	<.0001
					roseden	-0.051	0.0207	-2.46	0.0141
					pctwater	0.029	0.0111	2.66	0.0079

Table 3.6. Final multivariate model for gravid traps.

	Binary Model				Count model				
Variable	Estimate	SE	t-value	P-value		Estimate	SE	t-value	P-value
avgtempc	0.2366	0.0418	5.66	<.0001	avgtempc	0.1115	0.0239	4.66	<.0001
precilag4	0.1295	0.0334	3.88	0.0001	avgtemplag1	0.1109	0.0249	4.45	<.0001
humiditylag1	-0.0412	0.0156	-2.63	0.0086	avgtemplag3	0.0641	0.0216	2.97	0.003
pctmmc	0.0135	0.0047	2.85	0.0045	avgtemplag4	-0.0959	0.0209	-4.57	<.0001
mapleden	-0.0234	0.0087	-2.68	0.0075	precilag2	0.0967	0.0158	6.1	<.0001
					precilag3	-0.0389	0.0154	-2.52	0.0119
					precilag4	0.0631	0.0148	4.26	<.0001
					avgwindlag3	0.0697	0.0226	3.08	0.0021
					avghumidity	-0.0347	0.0079	-4.37	<.0001
					mapleden	-0.0232	0.0082	-2.82	0.0049
					pctwooded	-0.0049	0.0023	-2.06	0.0399

CHAPTER 4: ASSESSING HUMAN RISK OF ILLNESS WITH WEST NILE VIRUS MOSQUITO SURVEILLANCE DATA TO IMPROVE PUBLIC HEALTH PREPAREDNESS

4.1. ABSTRACT

Surveillance for West Nile virus (WNV) and other mosquito-borne pathogens involves costly and time-consuming collection and testing of mosquito samples. One difficulty faced by public health personnel is how to interpret mosquito data relative to human risk, thus leading to a failure to fully exploit the information from mosquito testing. The objective of our study was to use the information gained from historic West Nile virus mosquito testing to determine human risk relative to mosquito infection and to assess the usefulness of our mosquito infection forecasting models to give advance warning. We compared weekly mosquito infection rates from 2004 to 2013 to WNV case numbers in Illinois. We then developed a weather-based forecasting model to estimate the WNV mosquito infection rate one to three weeks ahead of mosquito testing both statewide and for nine regions of Illinois. We further evaluated human illness risk relative to both the measured and the model-estimated infection rates to provide guidelines for public health messages. We determined that across ten years, over half of human WNV cases occurred following the 29 (of 210) weeks with the highest mosquito infection rates. The values forecasted by the models can identify those time periods, but model results and data availability varied by region with much stronger results obtained from regions with more mosquito data. The differences among the regions may be related to the amount of surveillance or may be due to diverse landscape characteristics across Illinois. We set the stage for better use of all surveillance options available for WNV and described an approach to modeling that can be expanded to other mosquito-borne illnesses.[2]

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4.2. INTRODUCTION

West Nile virus (*Flaviridae: Flavivirus*) is a multi-host mosquito-borne pathogen that was introduced in the United States in 1999. Since then, more than 43,000 cases of human West Nile Virus (WNV) cases have been reported countrywide (CDC, 2016). The state of Illinois, where our study focuses, reported more than 2,200 cases between 2002 and 2015, with about three-fourths of cases occurring in just four of the fourteen years: 2002 (884 cases), 2005 (252 cases), 2006 (215 cases) and 2012 (290 cases) (CDC, 2016). In nature, West Nile virus is maintained through a complex enzootic cycle involving wild birds as the reservoir hosts and mosquitoes (primarily *Culex* sp.) as the vectors (Lanciotti et al., 1999; Hamer et al., 2008a). Occasionally, WNV spills over and infects mammals, especially horses and humans (Murray et al., 2010). Only about 20-30% of infections develop into acute febrile illnesses, and less than one percent develop a severe neuro-invasive form of the disease (Hayes and Gubler, 2006).

Monitoring of WNV circulation is crucial for early detection of outbreaks in the human population, but common surveillance methods have advantages and disadvantages. Reported cases of human and equine illness may come too late to inform critical early decisions about vector control, and they can be affected by reporting bias (Brownstein et al., 2004). Dead bird testing and the use of sentinel chickens are useful for early detection of WNV, but they are expensive, have limited geographical meaning, and can be difficult to equate to WNV risk in the human population (Komar, 2001). Vector mosquito collection and testing is the most practical and commonly used surveillance method (Kilpatrick & Pape, 2013). The costs and expertise required can be significant, but mosquito control is a recognized public health function, and institutional support is usually available in more populated regions (Healy et al., 2015). Mosquito control is spatially variable, and may not be undertaken in resource-poor settings. Furthermore, communication of mosquito test results can be delayed, and this may interfere with timely implementation of regionally relevant WNV prevention measures (Shand et al., 2016).

Weather affects many aspects of *Culex* mosquito populations and their potential to transmit WNV. Higher temperature may increase mosquito production and the risk of WNV transmission by reducing the duration of the gonotrophic cycle, increasing the frequency of blood feeding, shortening the development time from egg to adult (Delatte et al., 2009), and enhancing virus replication within the vector (Dohm et al., 2002). Higher temperatures may also be associated with smaller adult mosquitoes that may be more susceptible to WNV as reported in other mosquito-virus systems (Alto et al., 2008). However, temperatures above 30°C can increase mortality of both immature and adult mosquitoes (Andreadis, 2012). Precipitation is likewise critical. Water is needed to create sites where mosquitoes breed (Strickman, 1988) but heavy rainfall can negatively impact mosquito abundance by flushing out larvae from aquatic sites (Gardner et al., 2012). Water added through anthropogenic activities can be especially important during dry periods (LaDeau et al., 2013).

Several prior studies have modeled the relationship between weather and infection in people and in WNV vectors (Landesman et al., 2007; Soverow et al., 2009; Ruiz et al., 2010; Little et al., 2016; Shand et al., 2016). Higher temperatures are often an important driver of increased risk in both people and vectors, but the relationship between precipitation and human WNV illnesses is complex and spatially variable. For example, human WNV cases were associated with above-average rainfall in the eastern United States and below-average rainfall in the western United States (Landesman et al., 2007). Weather conditions can also affect human behavior and outdoor activities schedules (Winters et al., 2008), thereby influencing the probability of contact between vector mosquitoes and people.

Disease forecasting models are a way to make use of relevant data to improve public health preparedness. Models to forecast human WNV illness have used data on mosquito abundance, the mosquito infection rate and vector index (a measure for human WNV risk calculated as the product of vector abundance and infection rate), crow densities, and past weather conditions (Table 4.1) (Eidson et al., 2005; Bolling et al., 2009; Kwan et al., 2012; Colborn et al., 2013; Kilpatrick and Pape, 2013; Manore et al., 2014; Chaintoutis et al., 2015; Healy et al., 2015). Among these measures, mosquito infection and vector indices have been the most commonly used and they provided warning of future illness several weeks ahead of human cases (Kilpatrick and Pape, 2013). However, across studies, the results were inconsistent making it difficult to develop recommendations for reliable public health indicators that are sensitive to local conditions using readily available data. Previous work in Illinois used weather to predict the mosquito infection rate (MIR) for one or two counties, but did not extend the models to the entire state nor did they determine how MIR is related spatially and temporally to human illness (Ruiz et al., 2010; Shand et al., 2016). Our objectives in this study are to: (i) determine public health risk relative to MIR in Illinois using a long term historic dataset, (ii) develop statewide and regional weather-based forecasting models of MIR in Illinois, and (iii) assess the potential for the weather-based MIR forecasted estimates to determine spatiotemporal risk of WNV to people.

4.3. MATERIALS AND METHODS

The study region comprises the state of Illinois and its nine climate divisions, as defined by the National Oceanic and Atmospheric Administration (https://www.ncdc.noaa.gov/monitoring-references/maps/us-climate-divisions.php) (Figure 4.1).

The 21-week time period from late May to late September (weeks 18 to 38) for the years from 2004 to 2013 was the primary temporal focus corresponding to ten years for which historic data were available.

Mosquito data

We obtained the results from mosquito pools tested in Illinois for WNV through a user agreement with the Illinois Department of Public Health (IDPH) from 2004 to 2013. These data were collated by the state from mosquito control and public health agencies across Illinois and were expected to follow a protocol developed by the state. This protocol indicates the testing of mosquito pools of up to 50 specimens, and agencies use an online portal to upload data to a central repository. In practice, agencies employ gravid traps to optimize the capture of oviposition seeking females, use antigen assays on all samples and use Real Time reverse transcriptase polymerase chain reaction (RT-PCR) when possible to confirm the positives identified by assay. When more than one test result was recorded for the same pool, only the RT-PCR results were used for the model. Among the pools used in the model and tested only by antigen assays, the VecTest accounted for 34% of the total tests and was more common in the earlier part of the study period. The Rapid Analyte Measurement Platform (or RAMP) test was used in 24% of the tests with broader use starting in 2008. RT-PCR was used for 42% of the pools, with the most consistent use in the Chicago region. Data used for the models included only pools of female *Culex* mosquitoes, with each pool coded positive or negative for WNV. We calculated the mosquito infection rate (MIR) for a given week and geographical region using the formula for the minimum infection rate: 1000 * (number of positive pools)/ (total number of mosquitoes in pools tested) (Biggerstaff, 2006). The weekly MIR was calculated for the state of Illinois and nine individual climate divisions to form a time series of 189 weeks for each region.

We also calculated the weekly normal MIR as the average weekly MIR for each region from 2005 to 2013. The “normal” MIR was subtracted from each weekly value to remove the major seasonal trend from the data used for the forecasting model.

Human illness data

We obtained the data for human WNV cases in Illinois through a user agreement with the Illinois Department of Public Health. These cases were defined by medical and public health personnel using the U.S. Centers for Disease Control and Prevention National Notifiable Diseases Surveillance System (NNDSS) Arboviral Diseases Case Definition, and they included all confirmed and probable cases reported to the Illinois-NDSSS with a reported date of onset during the study years. The data were aggregated by week of onset and county of residence to calculate the number of weekly human cases for each year from 2004 to 2013 for the state of Illinois and for the nine climate divisions.

Weather data

We obtained spatial climate data on the daily temperature and precipitation from 2004 to 2013 and the 30 years normal (1981- 2010) daily data from the Prism Climate Group (PRISM Climate Group, Oregon State University, http://prism.oregonstate.edu). The Prism data are from multiple weather monitoring networks, from which point data are modeled as spatial grids using interpolation and other statistical techniques. From the daily data, we calculated the weekly mean temperature from the seven daily averages for the state of Illinois and the nine climate divisions. Temperature data were further processed to measure a “Degree Week” (DW), which is the cumulative sum of the difference of a weekly temperature from the threshold value of 22°C. The baseline of 22˚C was selected based on a previous study as this value resulted in the highest temporal correlation between temperature and MIR (Ruiz et al., 2010). More specifically, for a given week, if the weekly temperature (T_{mean}) is greater than the threshold (T_{base}=22˚C), then $\Delta DW = T_{mean} - T_{base}$, otherwise 0. We calculated the weekly precipitation as a sum of the daily precipitation for that week and geographic region. Measures of seasonal temperature and precipitation for five prior seasons going back from the current year's spring season (March to May) to the prior summer (June to August) were calculated in a similar manner. As with the MIR values, all weather variables were calculated as differences from average, in this case the 30-year climate normal. This served to remove the seasonal trend from the data and allowed the models to focus on the variability that remained. Finally, we used average weekly length of day light hours to account for the variation in the mosquito activity based on photoperiod (US Naval Observatory, http://aa.usno.navy.mil/data/index.php).

Statistical methods

To assess the temporal relationship between MIR and human cases, we first examined all spatial and temporal patterns descriptively at the state and regional levels and reviewed the amount of mosquito surveillance effort across the state. We then used three different approaches to determine the temporal relationship between MIR and human illness. First, we examined the Spearman rank correlations between the number of human cases in a week and the MIR from one and two weeks earlier for each of the climate divisions and for the state during weeks 18 to 39 from 2004 to 2013. Second, we compared six ranges of the weekly measured MIR (0, 0- 1, 1-2, 2-3, 3-4, >4) to the number of human WNV illnesses reported at a one-week lag within a region and time period, with intention to develop WNV risk categories that could be used by public health agencies. Third, we examined the mean MIR across a six-week period in the mid-summer (July to mid-August) and compared this to the number of human WNV illnesses for the full year. For this analysis, we evaluated linear equations where the mid-season MIR was regressed on the number of human cases, and the R^2 and predictive R^2 were used to evaluate the explanatory and predictive power of models with this single variable.

To develop the weather based MIR forecasting models, the weekly MIR was the dependent variable. The explanatory variables were the temperature from one-to-four weeks lag, weekly precipitation from one-to-four weeks lag, interactions of weekly temperature and precipitation lags, and the quarterly temperature and precipitation for spring, winter, fall, last summer and last spring. The list of variables is presented in Table A.1 (Appendix A), and is an extension of previously published work (Shand et al., 2016). A set of stepwise multiple linear regression models were used to develop the statistical model and the top ten competing models were selected based on the Akaike information criterion (AIC). The models within AIC values of 2 were considered competing models (Posada and Buckley, 2004). Finally, model averaging was performed to obtain the average parameter estimates from selected competing models and used for predicting the MIR. The comparison of models among regions was done with standardized parameter estimates. The statistical analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary) and R 3.3.1 (R Core Team 2016).

4.4. RESULTS

For the ten years combined, the highest average MIR (4.63) was in Climate Division (CD) 2, and the lowest average MIR (0.60) was recorded in CD 9. The highest rate of human cases of illness of 10.42 / 100,000 (913 cases) was also reported in CD 2. CD 3 had the lowest rate at 2.01 and the least number of cases (5) (Table 4.2). Trapping effort and testing varied significantly across the nine climate divisions during the study period (Figure 4.1, Table 4.2 and Table A.2). The most intensively surveyed region (CD 2) had an annual average of 480 traps and about 12,000 *Culex* mosquito pools tested each year. In contrast, in CD 7, an average of 18 traps were set out each year with about 85 *Culex* mosquito pools tested annually.

At the state level the first positive mosquito pools were recorded on average 6.8 weeks prior to the first human infection, but this interval was much shorter in CD 1 and CD 9, with 3.3 weeks and 3.8 weeks respectively (Table 4.2). Examining the week of the first positive pools and the first cases of illness for the full state and the nine regions for ten years (100 instances), a record of mosquito infection usually preceded the first human cases, but in 10 instances, human cases were reported before positive mosquitoes were found within a region. In 24 instances, positive pools were seen, but no illness was recorded.

The number of weekly cases of reported WNV illnesses and the measured MIR two weeks earlier were highly correlated at the state level ($r = 0.787$) and for CD 2 ($r = 0.821$) with similar correlations at one week earlier. For almost all CDs, the value of MIR at one to two weeks prior was significantly correlated with the number of WNV cases, but the strength of the relationship varied (Table A.3).

Comparing the six classes of MIR severity to the cumulative percentage of human WNV cases in the full state of Illinois over 210 weeks, 34.3% of the cases occurred in the weeks following the 13 weeks (6.2%) when MIR was greater than 4.0, and 53% of cases followed the 29 weeks (13.8%) when MIR was greater than 3.0 (Table A.4). At the state level, none of the human cases were reported after the 26 weeks when MIR was 0. Overall, over 92% of the Illinois human cases occurred during the 39% of the weeks when the average statewide MIR one week prior was higher than 1.0 (Table A.4).

The mid-summer MIR accounted for 69% of the variation in the total annual human WNV cases in Illinois (Table A.5). Regionally, the predictive value of mid-summer MIR was strongest in CD 2, with 0.921 explanatory and 0.899 predictive R^2, but only three other CDs showed an appreciable predictive value of this factor (Table A.5).

The weather-based MIR prediction model for the full state of Illinois explained 54% of the variation in the measured weekly MIR. The weekly lagged temperature and their interactions with lagged weekly precipitation up to one month were stronger predictors of WNV MIR compared to prior seasons' weather (Table A.6). However, a cold fall, warmer and dry winter, and warmer and wet spring were associated with higher weekly MIR during the summer in the statewide MIR model for Illinois (Table A.6). The predicted MIR captured the amplitude of most years, but tended to over-predict the early season, and did not capture the full measured MIR at its peak in some years (Figure 4.2).

The success of the MIR models for climate regions varied, with the highest adjusted R^2 value for CD 2 at 0.537. The next two strongest models were for CD 5 and CD 1 where 38.3% and 35.3% of the variation in the weekly MIR was explained respectively. The regions where the model explained less than 25% of the variability in the weekly MIR were located in the most rural, southern regions of Illinois (CDs 3, 7 and 9). The most important weather variables differed across the divisions (Table A.7, Figures A.1- A.6). The fall precipitation was the most consistent variable retained in the regional MIR models, with lower fall precipitation associated with higher MIR in five climate divisions in northern and central Illinois, and higher fall precipitation associated with higher MIR in southern Illinois. Lower precipitation in the spring and fewer daylight hours were associated with higher MIR in central and southern Illinois, but not in northern Illinois. The prior week's temperature was strongly associated with MIR in northern and central Illinois but not in southern Illinois, where interactions between temperature and precipitation were a stronger predictor than the individual temperature or precipitation variables. In all of the models, weekly precipitation by itself had modest influence on the MIR, but its interaction with temperature had a strong influence on MIR with variation in the magnitude and direction of the relationship across regions (Table A.7).

4.5. DISCUSSION

This study demonstrates how long-term mosquito surveillance data can be used to develop empirically based recommendations related to heightened public health risks from WNV in specific times and regions. It further illustrates how local estimates are required to capture the variable risk at different places, and how the region with the most data may dominate the statewide measures. Warnings of higher risk periods of WNV need to be implemented judiciously to maintain public attention and to encourage focused and efficient use of resources. Notably, in Illinois, relatively few weeks of the highest MIR (greater than 4) were of most concern for human WNV cases, while more than half of all weeks on record were weeks with very low to no MIR and represented a demonstrably low risk of illness. While we carried out the comparison of human illness relative to MIR only at the state level, it could also be done for separate regions. The highly populated northeastern Illinois counties near Chicago in CD 2 had both the highest average MIR of 4.63 and the highest WNV prevalence at 10.42 per 100,000 (913 cases). This region also had by far the most intensive surveillance and the remarkably strong pattern of illness relative to MIR as seen in both the high weekly correlation (r=0.821) and the predictive value of the 6-week MIR at mid-summer for human illness for that year (R^2 = 0.912). The climate region-based forecasting model in this area was not as strong (R^2 = 0.537) as the prior published models for just one or two counties. For example, the R^2 for a model of just Cook and DuPage counties (Ruiz et al., 2010), the R^2 was 0.80 and for the single county of

DuPage (Shand et al., 2016) it was 0.658. A county-level model may better serve the most populated counties in this region, but the surrounding counties in the CD may benefit more from the regional model.

In the less populated counties, there were generally lower MIR values and number of cases, and also less surveillance effort. CD 4 recorded the second highest overall MIR of 2.23 and reported 5.32 WNV cases per 100,000 (actual cases 39). CD 7 saw about the same WNV rate of 5.47 (actual cases 18), but recorded an average MIR of only 0.60 and also had the lowest number of traps collecting mosquitoes. In CD 7, the correlation between weekly MIR and human illness was modest ($r=0.241$, $p< 0.001$), but the weather forecasting model was not at all effective in this region. This region may benefit from additional monitoring of mosquitoes for WNV. The CD 9 had about the same number of traps as other rural divisions, while the number of mosquito pools tested was lower, which may indicate lower numbers of *Culex* mosquitoes in this region. More work is needed to determine how many traps are needed to detect mosquito infections most effectively, to account for the potential for underreporting of cases, and to consider a different modeling approach to help measure risk in rural areas where mosquito infection is present but relatively low. The combination of tests for WNV is a recognized weakness of our approach, but is a realistic reflection of data available from multiple agencies and one over which we had little control. RT-PCR is the most sensitive of the three testing approaches used in Illinois, but RT-PCR as well as the VecTest and RAMP tests are all considered sufficiently sensitive with pool sizes of 50 or less (Sutherland and Nasci, 2007). The use of the vector index to estimate risk by including mosquito abundance combined with the infection rate should be investigated, but this was not possible with the Illinois WNV mosquito testing dataset, which does not provide a measure of mosquito abundance.

The MIR in Illinois was influenced most strongly by the recent temperature and the interactions between temperature and precipitation up to one month prior, which is in agreement with the findings of prior studies (Chen et al., 2012; Shand et al., 2016). In addition, there was some seasonal effect; specifically with cooler falls, warmer and drier winters and warmer and wetter springs leading to higher MIR at the state level. Mild and drier winter conditions might improve survival of the *Culex* mosquitoes (Wimberly et al., 2014), while warm, wet springs might result in the earlier replication of the mosquitoes and serve to create water sources necessary for future mosquito breeding (Nelms et al., 2013). Dry weather in spring, as found by Little et al (2016) may give higher annual MIR by influencing the availability of stagnant water necessary for mosquito breeding (Little et al., 2016). The model differences observed across the Illinois CDs reflect the broad latitudinal and land use difference in the state. We suggest that possible approaches to improving the models for regions includes gathering more consistently dense data in all parts of the state to gain a more accurate measurement of MIR, and developing models that include landscape features in addition to the weather factors.

In summary, our analysis revealed several important relationships between mosquito infection rates and the occurrence of human WNV illnesses in Illinois. The provision of this information to public health officials will help them to gain more intelligence from the changes in MIR and the future risk of WNV illness. We suggest that it is possible to categorize weeks into risk levels based on prior empirical relationships, and that the forecasting models can help to indicate the risk level of upcoming weeks. The forecasting model we developed used freely available weather data and past mosquito infection data, and is a relatively simple approach that can be tailored for use by local public health agencies to predict the following week's MIR as an important supplement to ongoing testing for WNV. Though these models do not reflect the exact status of mosquito infection, they give an earlier indication of possible mosquito infection peaks and will be especially useful when resources are limited for mosquito testing. Finally, we demonstrated both the potential of and made suggestions for improving the models, thus setting the stage for better use of all surveillance options available for WNV and an approach to modeling that can be expanded to other mosquito-borne illnesses.

4.6. FIGURES AND TABLES

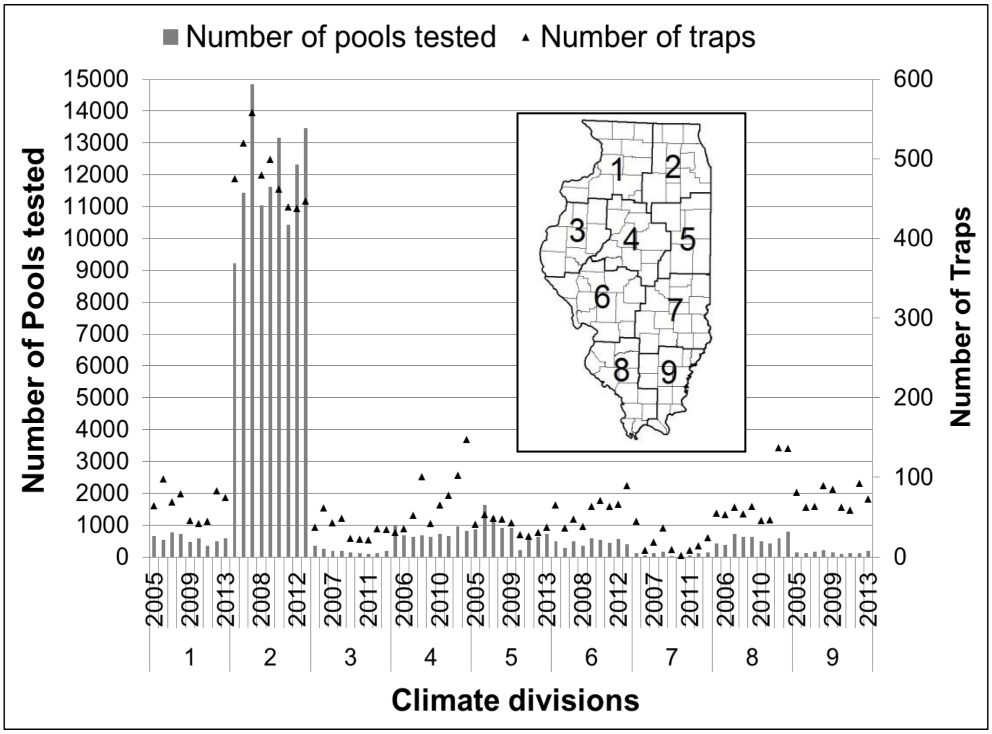

Figure 4.1. *Culex* mosquito surveillance activities in climate divisions of Illinois from 2005 to 2013. The map in the inset shows climate divisions in Illinois.

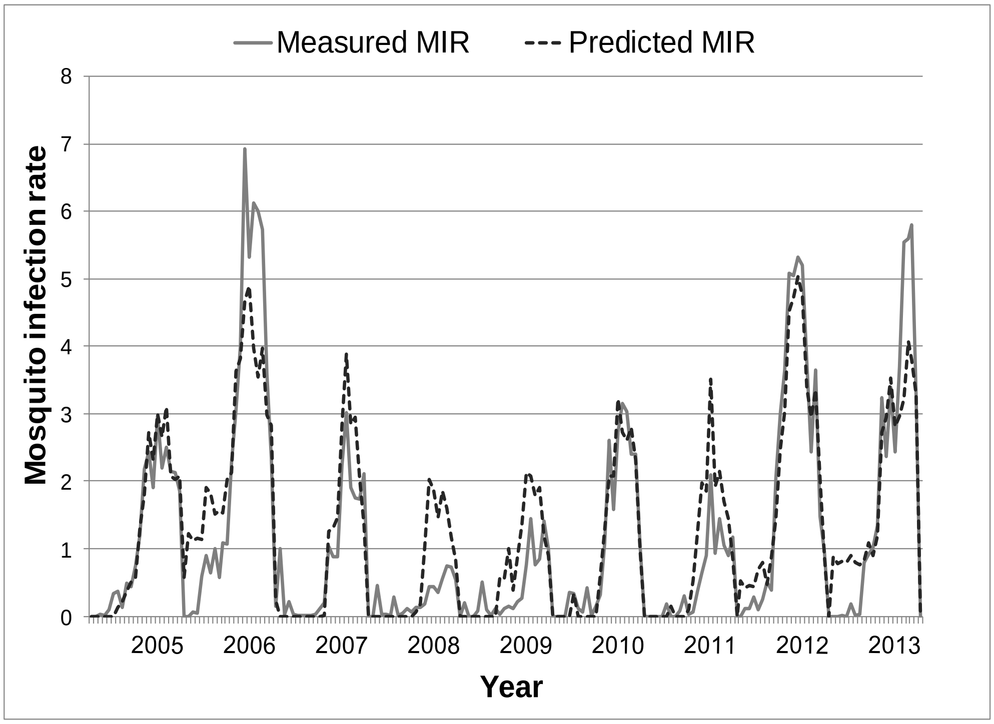

Figure 4.2. Measured (solid) and predicted (dotted) mosquito infection rate (MIR) in Illinois from 2005 to 2013 during the summer seasons (weeks 18 to weeks 38).

Table 4.1. Risk indicators, forecasting lag, and area of prediction for modeled estimates of the risk of human WNV illnesses.

Risk indicator	Time lag before onset of human cases	Geographic area (scale)	Reference
Dead crow densities: above threshold of 0.1 dead crows/ square mile	Current week or 1-2 weeks	New York (Counties)	(Eidson et al., 2005)
Seroconversion in chickens	1.5 months	Greece (Regional units and municipalities of Central and Eastern Macedonia)	(Chaintoutis et al., 2015)
Mosquito infection	Several weeks	Colorado (Statewide and Counties)	(Kilpatrick & Pape, 2013)
Environmental and demographic variables: higher minimum temperature in January	5-6 months	US (Counties)	(Manore et al., 2014)
Dead bird testing	5 weeks	California (Mosquito and vector control districts)	(Healy et al., 2015)
Mosquito infection	2 weeks		
California mosquito-borne risk assessment (CMVRA), vector index (VI) and Dynamic continuous area-space-time system (DYCAST)	CMVRA > 2.6 threshold was best as it was able to detect human cases at least 2 weeks in advance for most of the years.	California (Los Angeles County)	(Kwan et al., 2012)
Cx. tarsalis abundance and vector index	*Cx. tarsalis* abundance 4-7 weeks and vector index 1-2 weeks	Colorado (Northeastern five Counties)	(Bolling et al., 2009)
Vector index	2 weeks	Arizona (Maricopa County)	(Colborn et al., 2013)

Table 4.2. Annual average trapping effort, average mosquito infection rate (MIR) and total human West Nile virus (WNV) cases from 2005 to 2013.

Climate division	Average annual Number of traps (SD)	Average Number of pools tested (SD)	Average MIR (SD)	Human cases and rate per /100,000	Average weeks between first mosquito infection and human case
Northwest (1)	64.4 (19.5)	577.3 (128.8)	0.69 (0.61)	30 (3.83)	3.3
Northeast (2)	479.4 (40.2)	11947.8 (1703.2)	4.63 (3.82)	913 (10.42)	7.1
West (3)	36 (13.2)	186.6 (80.5)	0.82 (0.86)	5 (2.01)	7.8
Central (4)	72.2 (38.4)	753.4 (137.7)	2.26 (1.73)	39 (5.32)	7.7
East (5)	39.2 (9.6)	859.2 (408.4)	1.69 (1.47)	15 (3.03)	9.7
West southwest (6)	59.7 (16.8)	464.6 (101.2)	0.89 (0.82)	28 (3.94)	6.0
East southeast (7)	18.1 (14.1)	84.7 (58.8)	0.60 (0.89)	18 (5.47)	6.0
Southwest (8)	72.3 (36.8)	565.4 (145.4)	0.84 (0.61)	29 (4.97)	7.5
Southeast (9)	73.7 (13.1)	149.4 (38.4)	0.91 (1.14)	14 (7.29)	3.8

SD= Standard deviation

CHAPTER 5: THE DRIVERS OF WEST NILE VIRUS HUMAN ILLNESS: FINE SCALE DYNAMIC EFFECTS OF WEATHER, MOSQUITO INFECTION, SOCIAL, AND BIOLOGICAL CONDITIONS

5.1. ABSTRACT

West Nile virus (WNV) has consistently been reported as human cases of illness and infected mosquitoes in the region near Chicago, Illinois. However, the number of cases of human illnesses and the rate of WNV mosquito infection varies across years, with intermittent outbreaks. Several dynamic factors, including temperature, rainfall, and infection status of vector mosquito populations are responsible for much of these observed variations. But these temporally changing factors are mitigated by the local landscape structure and human demographic characteristics. The geographic and temporal scales used to analyze such complex data affect the observed associations. Here, we used spatial and statistical modeling approaches to investigate the factors that drive the outcome of WNV human illness on fine temporal and spatial scales, Our approach included multi-level modeling and long-term weekly data from 2005 to 2016 with weekly measures of mosquito infection, human illness and weather, combined with more stable landscape and demographic factors and with the geographical scale based on 1000m hexagons. We found that hot and dry weather conditions and higher MIR in earlier weeks and higher percentages of the white population increased the probability of an area of having a WNV human case. The higher proportion of high and medium intensity urban areas and open water sources in an area decreased the probability of observing a WNV human case. Additionally, we found that cumulative positive mosquito pools up to 31 weeks can strongly predict the total annual human WNV cases in the Chicago region. This study helped us to improve our understanding of the fine-scale drivers of spatiotemporal variability of human WNV cases.

5.2. INTRODUCTION

West Nile virus (WNV), a mosquito-borne zoonotic disease, was first identified in the United States in the summer of 1999 in New York City (Lanciotti et al., 1999). The mosquitoes of several *Culex* species are the primary enzootic and bridge vectors for the transmission of WNV, and several bird species are known to contribute in the amplification of the virus (Kilpatrick et al., 2007; Hamer et al., 2008a; Hamer et al., 2008b). Since its first successful invasion in New York, WNV quickly adapted to the local populations of *Culex* vector mosquitoes and avian populations and rapidly spread throughout the conterminous United States (Hayes and Gubler, 2006; Brault, 2009). The first major WNV outbreak in the United States was observed in 2002, when more than 4,150 human cases and 284 deaths attributable to WNV infection were reported to the CDC from 40 states -- compared to only 149 cases and 19 deaths from 10 states cumulatively during the three years from 1999 to 2001 (CDC, 2017). This stirred a prompt public health response from federal, state, and local public health agencies and led to the establishment of a more robust surveillance of mosquitoes and birds to monitor and control the spread of WNV (Marfin et al., 2001).

Public health surveillance for West Nile virus (WNV) involves: collection and testing of *Culex* vector mosquitoes; collection and testing of dead birds suspected to have died of WNV; testing of sentinel chickens or of wild birds captured for this purpose; and reported cases of human and equine illness (Lindsey et al., 2010). The ultimate goals of these surveillance data are to reduce illness through targeted mosquito control through the reduction of the number of infected vector mosquitoes and via effective educational messages to warn citizens to reduce individual exposure. One additional advantage of having a strong surveillance system in place is that the long-term data generated can be integrated with publicly available weather, landscape, and socioeconomic data and can be used effectively to identify the important drivers of WNV transmission and to develop predictive models (Kilpatrick and Pape, 2013; Manore et al., 2014).

Several earlier studies have identified some of the important drivers of WNV transmission in humans. These factors include prior weather conditions and landscape structure that affect the mosquito's biological responses, the abundance and infection status of the vector mosquitoes, demographic and social characteristic of population, individual human behavior, and the level of public awareness (Ruiz et al., 2004; Kilpatrick and Pape, 2013; Manore et al., 2014; Roiz et al., 2014; Rosà et al., 2014; Wimberly et al., 2014; Hahn et al., 2015; Giordano et al., 2017). For example, the analysis of 12 years of mosquito testing and human illness data in Ontario, Canada showed that the mosquito infection rate of one week earlier was the strongest temporal predictor of human risk of WNV. They further established an epidemic threshold based on the cumulative positive *Culex* pools up to mid-August (week 34), which can be successfully used to predict human WNV epidemics (Giordano et al., 2017). In Long Island, New York, more than 65% of forecast models based on past mosquito infection and human illness correctly predicted seasonal total human WNV cases up to 9 weeks before the first reported cases (DeFelice et al., 2017). Similarly, the vector index, based on a combination of vector infection and abundance was found to be highly correlated with human WNV cases in studies conducted in Larimer County, Colorado (Fauver et al., 2015), and Dallas, Texas (Chung et al., 2013).

Weather factors are important drivers of WNV transmission due to their direct effect in mosquito biology. When compared with human WNV cases, higher than normal average annual temperature are associated with an increased likelihood of higher WNV disease incidence, nationally and in most regions in the United States (Hahn et al., 2015). This relationship was true in Europe too where abnormal July temperature was associated with higher incidence of human

WNV cases (Tran et al., 2014). The role of precipitation is often controversial and varies by study regions. For example, higher than normal precipitations was positively associated with higher human WNV cases in the eastern region of the United States, but this relationship was opposite for the western region (Landesman et al., 2007). Another study identified drought as an important driver of WNV epidemics in the United States (Paull et al., 2017). The local landscape structures have also been associated with human WNV incidence. The important land cover variables identified to be associated with increased risks of human WNV include proximity to wetlands (Chuang et al., 2012; Sallam et al., 2017), higher tree density (Sallam et al., 2017), rural irrigated and agricultural areas (DeGroote and Sugumaran, 2012), and urban areas characterized by higher impervious surfaces and storm sewer system (Liu et al., 2011), and inner suburbs characterized by older houses, moderate vegetation and moderate population (Ruiz et al., 2007).

Apart from extrinsic factors, population structure, demographic characteristics, and individual variation also play roles in WNV epidemics (Brinton, 2001). As people age and especially when they have a history of hypertension and immunosuppression, they have an increased risk of acquiring a WNV infection (Nolan et al., 2013; Montgomery and Murray, 2015). Community characteristics such as income level, the age of housing, and management of sewer and drainage system, mosquito abatement practices, and public health infrastructure also determines the risk of WNV human infections (Ruiz et al., 2004; Liu et al., 2011).

Different spatial scales have been used in geographical analyses to identify the drivers of human risk from WNV infections. The most commonly used spatial scale in the United States is counties (Hahn et al., 2015; Davis et al., 2017; Paull et al., 2017), census tracts or Zip Code Tabulation Areas (ZCTA) (Ruiz et al., 2004; Wimberly et al., 2013), census block groups (DeGroote et al., 2008), and buffers of varying sizes around trap locations or human cases

(Sallam et al., 2017). Each of these spatial scales has its own inherent biases, as these political boundaries do not necessarily correspond to the ecological processes of the disease in question (Kwan, 2012). Alternatively, dividing the area into equal spaces such as rectangular or square bins, and hexagons have been used to reduce some of these biases (e.g. Ruiz et al. 2010). Hexagonal grids have an additional advantage that they reduce the edge effects, better fit the curved surfaces, and have identical neighbors (Birch et al., 2007; Potter et al., 2016).

In Illinois, there has been a consistent presence of WNV human infections since 2002, with annual variability in the number of cases (IDPH, 2017). The majority of the human WNV cases have been reported from the northeastern region, where the largest number of people in the state is congregated. A census tract level analysis in this region using human WNV occurrence data from the 2002 outbreak year identified that census tracts with lower population density, relatively close WNV positive dead bird specimens, higher percentage of older, white residents, and housing built between 1950- 1959 were more likely to characterize areas in spatial clusters of WNV cases (Ruiz et al., 2004). A follow up to this northeastern Illinois study re-examined these relationships using data to develop annual models of WNV human illness from 2002 to 2006, but with additional variables to assess the effects of rainfall, temperature and the WNV mosquito infection rate (Messina et al., 2011). This analysis determined that white populations and housing from the 1950s were associated in some years; this was not true in all years. Further, census tracts with lower rainfall had higher rates of WNV illness, but the mosquito infection rate was not an important variable in any of the models (Messina et al., 2011).

Despite the identification of some of these potential risk factors, the dynamic nature of spatiotemporal variability of human illness cases from WNV remains elusive at the local scale, especially as it is related to dynamic weather and mosquito infection status. Now, with the availability of long-term data on human WNV illness and intensive mosquito surveillance for the Chicago region, we can use these to identify the fine scale drivers of spatiotemporal variability of human WNV epidemic in an urban environment. The overall goal of this study is to determine factors affecting the spatiotemporal variability of risk for transmission of WNV to humans through identification of the fine scale drivers of WNV transmission. These factors include dynamic mosquito infection and weather in an urban area with a repeated history of WNV outbreaks. Our specific objectives in this study are to (i) describe the fine-scale temporal and spatial patterns of human WNV illness in the Chicago region, (ii) evaluate the temporal relationships between mosquito infection and human WNV illness, and (iii) determine the fine-scale dynamic effects of weather, land cover, mosquito infection, and demographic factors on the presence of human West Nile virus illness across time and space.

5.3. MATERIALS AND METHODS

The two Illinois counties of Cook and DuPage, comprising Chicago and its suburbs, were included in this study. The total area covered by these two counties is nearly 5,100 square kilometers, and the total population in 2010 was 6.1 million. These areas were selected because of the concentration of human West Nile virus illness in Illinois reported from these two counties and the long-term intensive mosquito surveillance data available for this region. The temporal window included in this study was the 24-week time-period from late May to late October (weeks 22 to 45), which corresponds to the timing of mosquito activity and human WNV illness, with data for the years from 2005 to 2016. The years from 2002 to 2004, during which Illinois had its first invasion from WNV, were excluded in this analysis because of the absence of mosquito testing data.

We chose to summarize all variables into hexagons to provide a neutral spatial unit of consistent size and shape, which is not possible with political boundaries. For this, we overlaid hexagons measuring 1000 m across on the outlines of Cook and DuPage counties to create a grid of 5,345 hexagons for the study area. Out of these, 328 were excluded after a comparison with fine scale population data from the 2010 U.S. Census, indicated that there were no households on record within those hexagons. Thus, 5,017 hexagons were included in the analysis. All the independent variables related to weather, land cover, mosquito infection and demography were calculated for each hexagon, as described below.

Mosquito data

The mosquito testing data from 2005 to 2016 were obtained from the Illinois Department of Public Health (IDPH) through a user agreement. The IDPH collates the data from local public health agencies and mosquito abatement districts across Illinois and maintains a statewide database for the results from WNV mosquito testing. The IDPH developed and promotes a mosquito surveillance protocol, and local health and mosquito abatement districts are expected to follow this protocol in order to standardize the mosquito collection and testing across the state. In general, the local agencies collect vector mosquitoes with gravid traps, identify the sex and species of the mosquitoes, and make pools of up to 50 mosquitoes from those captured in each trap to test for the presence of WNV infection. When fewer then 50 mosquitoes are captured, a pool will consist of fewer than 50 mosquitoes. During the study period, the common tests used to identify WNV in mosquitoes included the antigen assays - VecTest or Rapid Analyte Measurement Platform (RAMP) test. Some pools were tested by Real Time reverse transcriptase polymerase chain reaction (RT-PCR). In instances when a pool was tested using more than one type of test, only the RT-PCR results were used in the analysis. Our analysis used only the test results from pools of female *Cuelx* mosquitoes.

To determine the location of the mosquito traps, we used the existing latitude and longitude recorded in the IDPH database. In cases where the spatial data were missing, we geocoded the trap locations based on the address provided. Our analysis used all the trap locations recorded from 2005 to 2016 from Cook and DuPage counties and as well as from five surrounding counties; namely, Lake, McHenry, Kane, Kendall, and Will. For each trap, the mosquito infection rate (MIR) was calculated by week and by year using the formula: 1000* (number of positive pools)/ (total number of mosquitoes in pools tested) (Biggerstaff, 2006). From all the traps within Cook and DuPage counties, in addition to traps located within a 10 km radius from their boundaries, we developed continuous surface maps for MIR for each week and year using an inverse distance weighting (IDW) interpolation technique in ArcGIS 10.1. From this interpolated surface map for each year and week, the average, minimum, and maximum MIR for each hexagon was calculated using the Zonal statistics as table function in ArcGIS 10.1. A model builder platform using iteration features in ArcGIS 10.1 was used to run these processes.

Human illness data

The human WNV cases in Illinois were obtained from the IDPH through a user agreement. All confirmed and probable cases of WNV reported to the IDPH by medical and public health personnel for the study area were included in this study. All the human WNV cases in Cook and DuPage counties reported from 2005 to 2016 were geocoded, and aggregated by hexagons for each week and year. As only a few hexagons had more than 1 case in any given week and year, the data were converted into the binary form as presence or absence of a WNV case in a given hexagon and week.

Demographic data

The demographic data included were total population, racial composition, and income level. The total population and racial composition included the number of White, African American, Asian, and Hispanic people from census block level data from the 2010 U.S. Census. The income data for the block group level were obtained from the 2015 American Community Survey. These demographic data were processed in ArcGIS using the intersection tool to calculate a parameter for each hexagon. Finally, the racial population data was converted as the percentage of White, African American, Asian, and Hispanic people in each hexagon.

Landcover data

The landcover data for the entire United States was obtained from the national landcover database (NLCD) for the years 2006 and 2011. The NLCD database is a Landsat based landcover data available at a 30 m resolution (www.mrlc.gov). The landcover raster was clipped for Cook and DuPage counties including a 1 km buffer surrounding them. From this clipped raster, the total number of pixels for each land category within each hexagon was calculated using the tabulate as area tool in ArcGIS 10.1. The proportion of each land cover category for each hexagon was then calculated by dividing the number of pixels for that category by the total number of pixels for all categories. In Cook and DuPage counties, 15 different types of landcover were available that include urban areas (developed open space, developed low intensity, developed medium intensity, developed high intensity), forests (deciduous, evergreen and mixed), barren land, shrubs, grassland, pasture, cultivated crops, woody wetlands, herbaceous wetlands, and open water. The land cover data from 2006 was used to analyze the WNV cases for the years from 2006 to 2010, while the land cover data from 2011 was used for 2011 to 2016.

Weather data

The spatial weather data on daily mean temperature and precipitation from 2005 to 2016 were obtained from the Prism Climate Group (PRISM Climate Group, Oregon State University, http://prism.oregonstate.edu). The Prism daily data are available as spatial grids of 4 km resolution, which are developed by the group through interpolation and statistical techniques using point data from weather monitoring networks across the country combined with topographic data. These daily data were used to calculate the weekly temperature and precipitation. For our analysis, the weekly mean temperature was calculated by taking the average of the seven daily averages for that week, and the weekly precipitation was calculated as a sum of the daily precipitation for that week. Finally, the weekly temperature and precipitation for each year and week for each hexagon was calculated by using the zonal statistics as table tool in ArcGIS 10.1.

Statistical methods

To assess the relationships between human illness and MIR, we first examined the temporal relationship alone. For this, we calculated the Spearman rank correlation between the weekly MIR of 1-6 weeks lag and human cases. We further divided the years into those with high numbers of WNV cases and those with low numbers of WNV cases to examine if the relationship between MIR and human cases varies in high and low years. The years that experienced more than 100 human cases were considered high years (2005, 2006, 2012 and 2016), while the years having less than 100 cases were considered low years (2007 - 2009, 2010, 2011, 2013 - 2015). We further examined the ability of the early summer (weeks 22- 27) and mid-summer (weeks 28- 33) MIR to explain and predict the seasonal annual total WNV cases by using regression analysis. In addition, we assessed the ability of the cumulative positive mosquito pools up to week 28 and thereafter added each week's data to find a threshold that could best explain the annual total human WNV cases. In both of these calculations, data from 2005 to 2014 were used to create a regression equation, and data from 2015 and 2016 was used to test the model.

To visualize the spatial patterns of human illness over time, we first, developed choropleth maps. Then, we used the spatial analysis software GeoDa to further identify the spatial clusters of cumulative human WNV cases from 2005 to 2016. For this, a local Moran's I method was used using an inclusive second order queen contiguity weight matrix. We also examined differences in results using neighboring cells and rook contiguity weight matrix but the results did not vary.

For the spatiotemporal statistical model, the outcome variable was the presence/ absence of a human WNV case in each hexagon for each year and week. The predictors included 32 variables related to weather, land cover, mosquito infection and demography (Table 5.1). The weather variables consisted of mean weekly temperature and precipitation from one-to-four weeks lag. The land cover variables include 15 categories that included the proportion of developed open space, developed low intensity, developed medium intensity, and developed high intensity urban areas, deciduous, evergreen and mixed forests, barren land, shrubs, grassland, pasture, cultivated crops, woody wetlands, herbaceous wetlands, and open water for each hexagon. The mosquito infection data included the average MIR of one-to-four weeks lags for each hexagon for each year and week. Among the demographic variables were the percentage of White, African American, Asian, Hispanic population within each hexagon, and the average median household income for each hexagon. In total, there were 1.44 million rows of data (5017 hexagons * 12 years * 24 weeks). The correlation matrix among all variables was created to evaluate multicollinearity before running the model. As our response variable was binary, we used mixed effects multiple logistic regression for the statistical analysis. In this approach, the log odds of the outcomes (presence or absence of WNV human cases) are modeled as a linear combination of explanatory variables. The hexagons were treated as a random variable. We used the PROC GLIMMIX procedure in the SAS statistical software. An Akaike information criterion (AIC) was used to choose the best model (Akaike, 1974). A receiver operating characteristics (ROC) curve was used to evaluate the model performance. The ROC curve is commonly used as a measure of a classifier performance and is considered adequate when the area under the curve is greater than 0.80. All the statistical analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary).

5.4. RESULTS

There were 1,371 total human WNV cases reported in Illinois from 2005 to 2016. Out of these total reported cases, 906 cases (66%) were from the Chicago region (Cook and DuPage Counties). There was an annual variation in the number of human WNV cases in the study region, with the year 2012 reporting the highest number of cases (229) followed by 2005 (181), 2006 (129), and 2016 (108 cases) (Table 5.2). The lowest number of cases was reported in 2009 (only 1 case) and 2010 (10 cases) (Table 5.2). The average annual MIR during the mosquito season was also highest for the outbreak year 2012 (7.34) followed by 2016 (6.34) and 2006 (5.35) (Table 5.2). The number of mosquito pools tested annually ranged from about 6,100 pools in 2016 to over 12,100 pools in 2007. Out of the total mosquito pools tested, 31.3% of the pools were positive for WNV in 2012 followed by 27.4% of the pools in 2016, and 27.1% of the pools in 2005 (Table 5.2).

We found a strong temporal relationship between the MIR of previous weeks and human WNV cases in the study region (Table 5.3, Figure 5.1). The strongest correlation was present when MIR of one week earlier (r= 0.837) was compared with weekly human case data of all years (2005- 2016) (Table 5.3). The strength of the correlation changed when high and low WNV years were delineated. In the high years (2005, 2006, 2012, and 2016), the weekly correlation was even stronger (r= 0.884), while the strength of the correlation was still strong, but relatively lower in low years (r= 0.737) (Table 5.3). When evaluated for only the 2012, when case counts were highest, the correlation was also the highest (r= 0.899) (Table 5.3). In both high and low years, the strength of the correlation gradually declined with lagged MIR and there was almost no correlation with MIR after lags of four weeks.

We found that the MIR of mid-summer (weeks 28-33) was able to explain 93% of the variability in total annual human cases (Table 5.4, Figure 5.2). The prediction equation applied for 2015 and 2016 estimated 44.8 human cases for 2015 and 142.7 human cases for 2016. The actual reported human cases were 35 for 2015 and 108 for 2016. Likewise, the cumulative number of positive pools also strongly explained and predicted the total annual human cases (Table 5.4, Figure 5.3). Specifically, the cumulative positive mosquito pools by week 31 can give a strong signal of how many total WNV human cases are going to occur by the end of the season, as it explained 93% of the variability in total annual human cases similar to that explained by mid-summer MIR (Table 5.4). The prediction equation developed using cumulative positive pools by week 31 predicted 35.1 human cases (35 actual cases) for 2015 and 102.8 human cases (108 actual cases) for 2016. The cumulative mosquito positive pools by week 31 thus better predicted the annual human cases than the mid-summer MIR.

The spatial pattern of human WNV cases in Cook and DuPage counties showed that the cases were distributed throughout most areas of the study region at some point during the study period, with some pockets of higher numbers of cases (Figure 5.4). Out of the total 5,345 hexagons in the study area, 750 hexagons had experienced at least one case of human WNV case during the years from 2005- 2016. Cumulatively, 123 hexagons had more than one human WNV case, with the maximum number of hexagons with a case being five (Figure 5.4). The local Moran's I identified some spatial clusters of human WNV cases in the Cook and DuPage counties (Figure 5.5). In total, 92 hexagons with higher numbers of cases were also near to others with higher numbers of cases, thus representing spatial clusters of WNV cases (Figure 5.5).

The results of the mixed-effects regression analysis showed that temperature, precipitation, land cover, mosquito infection, and demographic characteristics are all associated with the probability of an area having a case of WNV human illness. The AIC criteria used to compare the 10 best competing models showed that a model consisting of 13 variables that included temperature, precipitation, MIR, land cover, and demographic characteristics was the best model (Table 5.5). The final multivariable model indicated that higher temperature two, three and four weeks earlier were associated with the probability of a hexagon being positive for human WNV case (Table 5.6). The precipitation of two weeks earlier was negatively associated but was only moderately significant (Table 5.6). The lagged mosquito infection rate of one to four weeks earlier was positively associated with the outcome variable indicating that if the MIR of earlier weeks was higher, the probability of a hexagon being positive for human WNV would increase (Table 5.6). Among the land cover variables, the proportion of open water, and medium and high intensity developed areas were negatively associated with the outcome variable (Table 5.6). The percentage of the White population was the only demographic variable found to be positively associated with the outcome variable in the final model (Table 5.6). The ROC curve showed that the area under the curve was 0.913, which indicates that the model performance was excellent (Figure 5.6).

5.5. DISCUSSION

We identified important fine-scale drivers of spatiotemporal variability in the human WNV cases in Chicago region, Illinois, an area of ongoing WNV transmission. Our analysis used long-term data on human illness, mosquito surveillance, weather, landscape, and demographic data. We found significant spatial clusters of human WNV cases within this urban environment. We also found a strong correlation between the weekly MIR of earlier weeks and weekly human WNV cases, and further developed predictive temporal models using mid-summer average MIR and cumulative positive mosquito pools which can be used to estimate the total annual human WNV cases.

The temporal variation in the weekly human WNV cases was strongly correlated with MIR of one to four weeks earlier, with a correlation of one week earlier being the strongest. This finding was similar to our earlier finding based on Illinois climate divisions, where Division 2 includes our current study area (Karki et al., 2017). The similarity in the correlation may be due to the fact that the data for Climate Division 2 was dominated by the data from Cook and DuPage, as these counties have more intensive surveillance data available compared to other Illinois counties. Similar observations were found in Ontario, Canada where MIR of one week earlier was most strongly correlated with the weekly variation in human WNV cases (Giordano et al., 2017). In our study, we also found that the correlations between weekly MIR and human cases increases in high WNV years, and decreases in low years which was also observed in a study conducted in Long Island, New York (DeFelice et al., 2017). In addition, the temporal models we developed using mid-summer average MIR and cumulative mosquito positive pools were both able to explain more than 90% of the variability in the annual number of human cases. This result was not surprising as positive mosquito pools are used to calculate the MIR. But what was most interesting was that the cumulative positive pools up to week 31 better predicted the annual human cases compared to mid-summer average MIR for 2015 and 2016, the years that were not used in the model development. The predictive model using cumulative positive pools up to week 31 estimated 35.1 human cases for 2015 (36 actual reported), and 102.8 human cases for 2016 (108 actual reported), which were very close. The difference observed between the two approaches may be a reflection of the susceptibility of the MIR calculation depending on the mosquito pool size (Gu et al., 2003; Gu et al., 2004). Taking the most extreme possibility, when there was only one mosquito in a pool and it tested positive, this would yield an MIR of 1000 in contrast to MIR of 20 when a pool with 50 mosquitoes was tested positive. In Ontario Canada, the cumulative mosquito pools up to week 34 were suggested as an action threshold potential to estimate the total annual human cases (Giordano et al., 2017). In Chicago, we obtained this signal three weeks earlier, which can be crucial to the ability to intervene in the upcoming potential human WNV outbreak.

We found spatial clustering of human WNV cases within the study area using the local Moran's I statistical approach. This indicated that some areas were more likely than others to have a WNV human case. A spatial clustering pattern of human WNV cases in Chicago area was also observed in the 2002 WNV outbreak year (Ruiz et al., 2004). Several factors might play a role in the observed spatial clustering pattern that include differences in the fine-scale variation in the local landscape structure that affects mosquito population, fine-scale weather variation, demographic characteristics, access of people to health care system, and spatially variable mosquito abatement practices (Ruiz et al., 2004; Tedesco et al., 2010; Hamer et al., 2011; Messina et al., 2011).

In this study, through multilevel modeling, we identified several dynamic factors that are possibly driving the fine scale spatiotemporal variation in the human WNV cases occurrence in the Chicago region. We found that the higher temperature in the previous weeks increases the probability of an area being positive for a WNV case. The association between higher temperature and WNV human illness were also observed in other studies conducted at different spatial scales (Tran et al., 2014; Wimberly et al., 2014; Hahn et al., 2015). This is possibly due to the dynamic effect of higher temperature on mosquito breeding and virus replication (Reisen et al., 2006; Kilpatrick et al., 2008; Ruiz et al., 2010; Shand et al., 2016). The unique feature of our study is that by considering the dynamic nature of weather, we allowed the temperature and precipitation to vary both temporally and spatially to capture the better role of weather in the spatiotemporal variability of human WNV cases. The precipitation of earlier weeks was not as important as the temperature of the preceding weeks but still was moderately important. The negative association of precipitation observed indicated that dry and hot weather conditions would increase the probability of an area being positive for a WNV case. Some other studies have also indicated that hot dry weather conditions are conducive for WNV transmission (Epstein, 2001; Morin and Comrie, 2013).

We also found increased MIR up to four weeks earlier will increase the probability of an area being positive for a WNV human case. The temporal association between lagged MIR and human WNV cases is relatively well established (Kilpatrick and Pape, 2013; Mulatti et al., 2014; Giordano et al., 2017). However, it was interesting to find the positive association of MIR when both spatiotemporal variabilities of human cases were considered. In our current analysis, we found that the area with a higher percentage of the white population had a higher probability of being positive for WNV, which has also been observed in a previous study (Ruiz et al., 2004). This may be a function of some areas where people have better access to the health care system, are more likely to seek medical treatment and get tested (Ruiz et al., 2004; Ruiz et al., 2007) or may simply be due to the dominance of the white population in the areas of the study region where environmental conditions are also conducive to increased mosquito activity. Another interesting observation in the study was that the probability of a hexagon being a positive for WNV case decreased in developed medium and high-intensity urban areas, indicating that the suburban areas of Chicago are more at risk than the highly developed urban centers. The lack of mosquito breeding grounds and bird activity in the high-intensity urban areas might be responsible for this. Previous studies conducted in the same area have also indicated that sub-urban region in Chicago is at more risk from the WNV (Ruiz et al., 2004; Ruiz et al., 2007).

In summary, our analysis helped to better understand the fine-scale dynamic drivers of WNV transmission in an urban environment. The dynamic interplay between temperature and precipitation, mosquito infection, land cover, and demographic characteristics determine the probability of an area having a WNV case or not. Additionally, we established an important temporal relationship between cumulative mosquito positive pools and mid-summer average MIR with the total annual human WNV cases. This information can be used as a guideline to develop a threshold for public health intervention. In this study, we did not consider prior seasonal differences in the weather conditions and other important variables such as the age of housing which we recommend be incorporated in future studies. In addition, the calculation of MIR for hexagons may be biased as the IDW interpolation technique used to develop continuous surface maps are affected by the uneven distribution of mosquito traps across the study area. Alternatively, other interpolation methods such as kriging might be used to develop continuous surface maps for MIR as this method takes into account of spatial autocorrelation and also creates an error map. Here, we lumped both neuroinvasive and non-neuroinvasive cases together in this study. Separate analysis for only neuroinvasive cases only might help us to identify what conditions drive the occurrence of the severe form of WNV infection and should also help to reduce collection bias. Also, in future studies, we might consider using different spatial scales to identify if the geographic scale has affected the results.

5.6. FIGURES AND TABLES

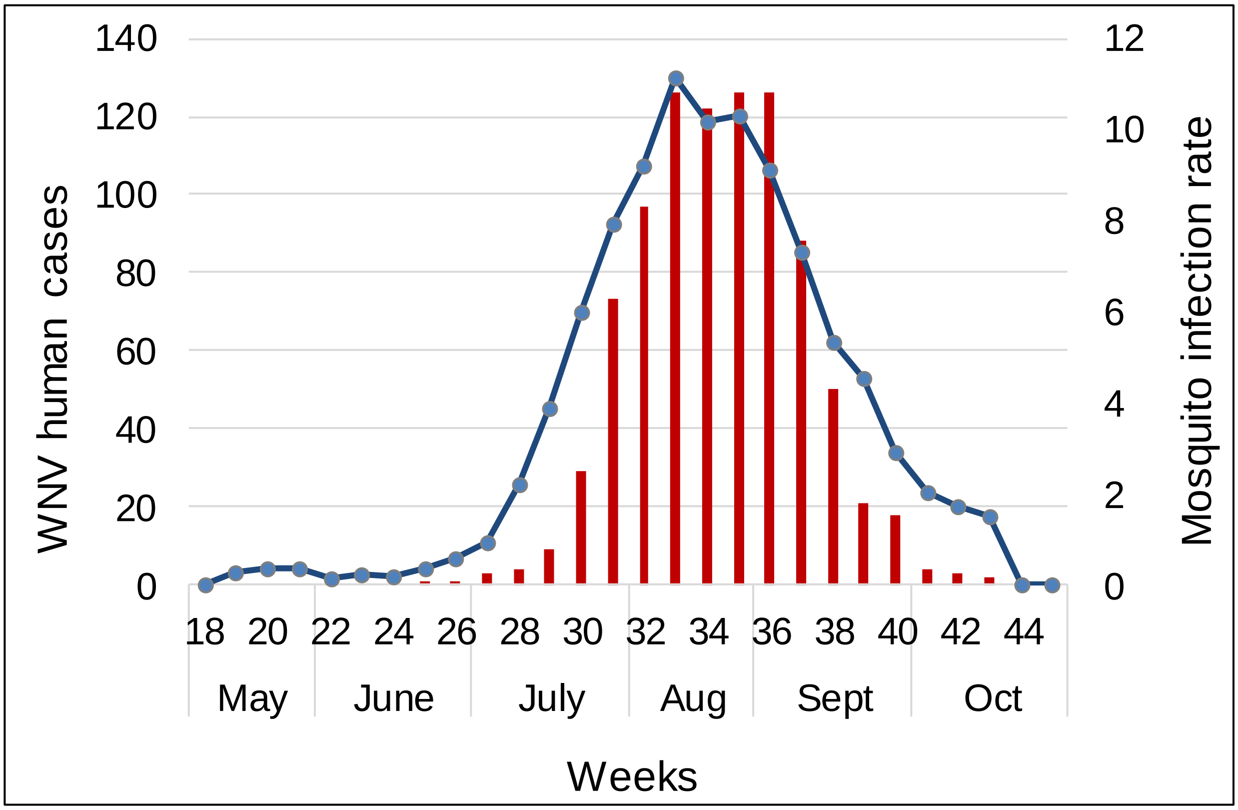

Figure 5.1. Cumulative weekly human WNV infections and mosquito infection rate from 2005-2016 in Cook and DuPage Counties, Illinois.

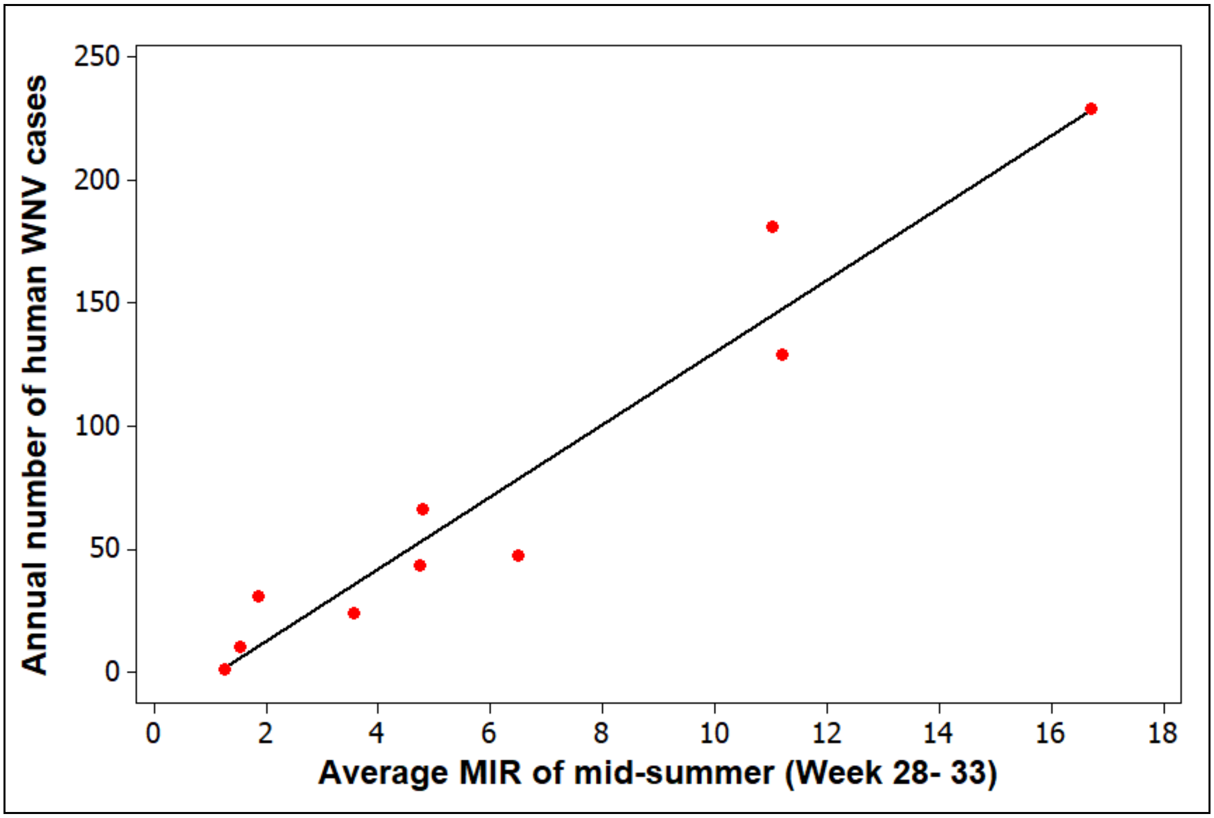

Figure 5.2. The relationship between annual human WNV infections and mid-summer mosquito infection rate from 2005- 2014 in Cook and DuPage Counties, Illinois.

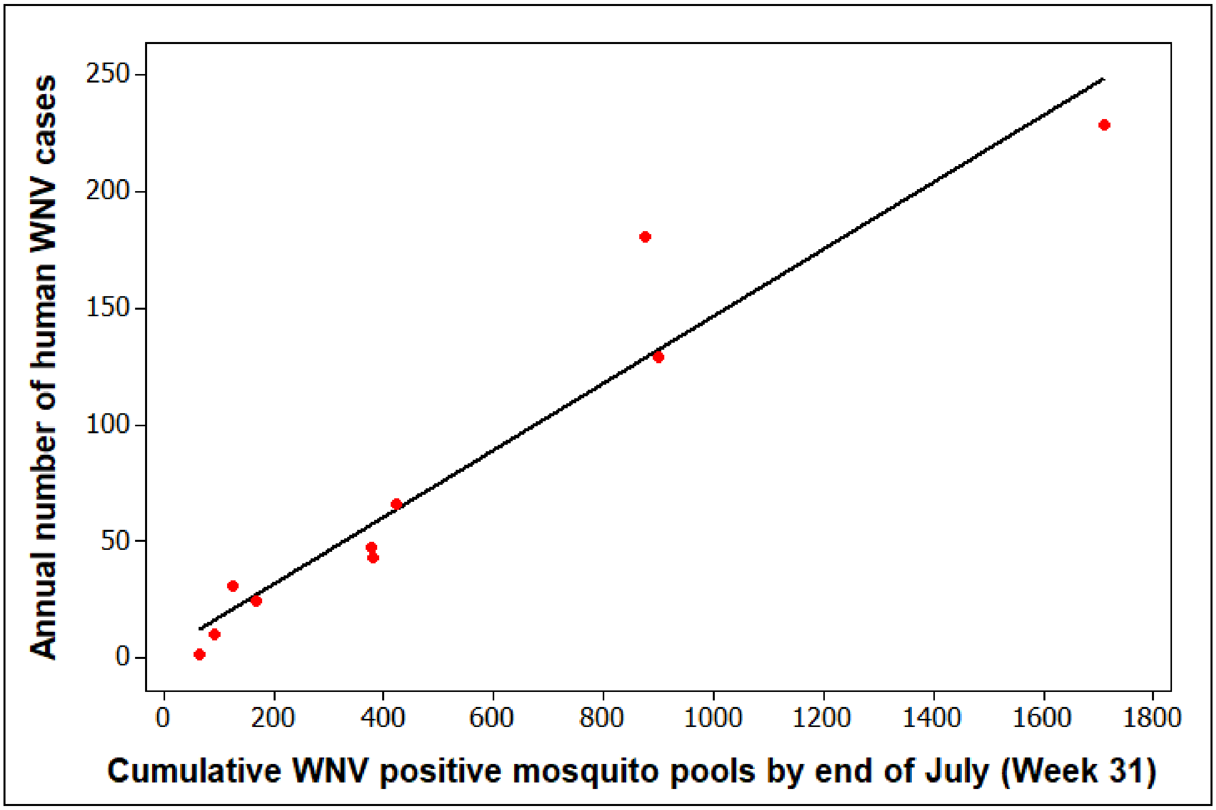

Figure 5.3. The relationship between annual human WNV infections and a cumulative number of WNV positive mosquito pools from 2005- 2014 in Cook and DuPage Counties, Illinois.

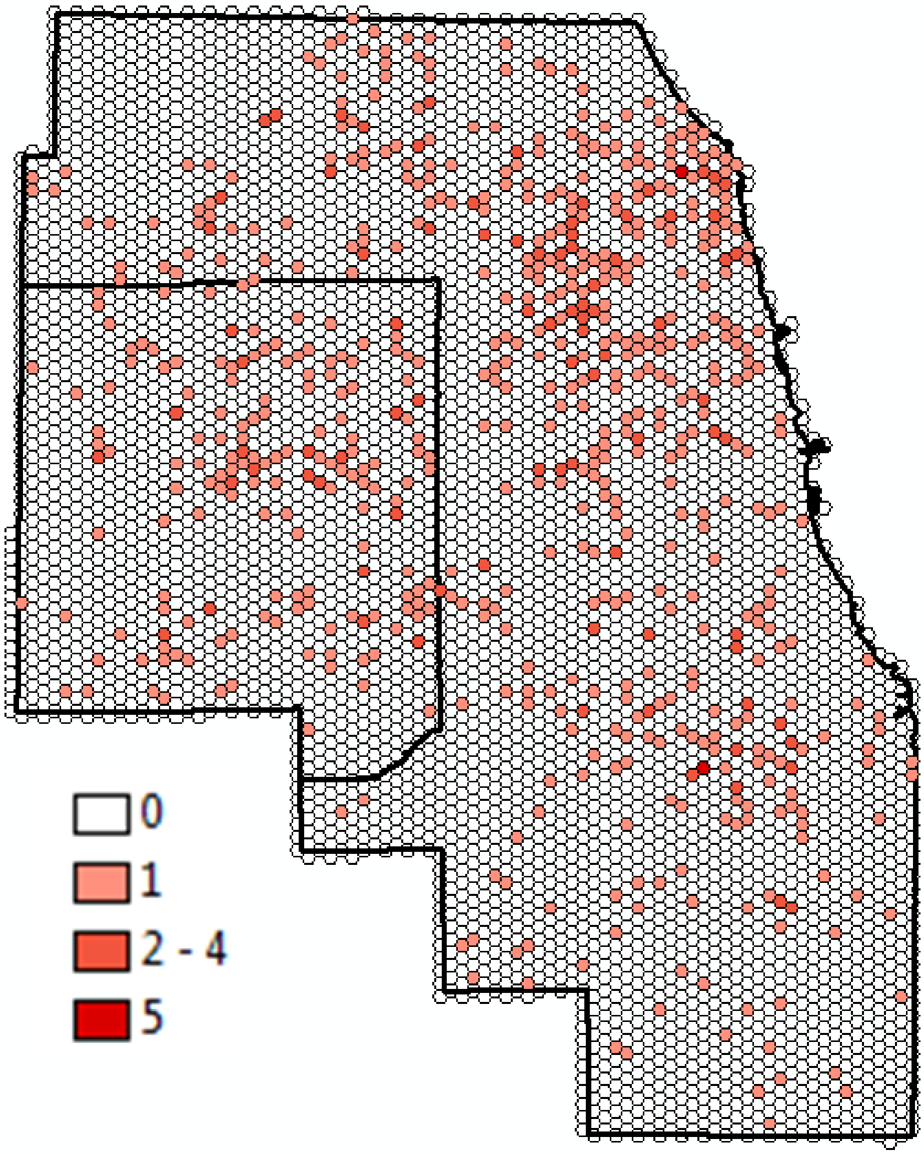

Figure 5.4. The spatial distribution of the cumulative number of human WNV infections from 2005- 2016 in Cook and DuPage Counties, Illinois.

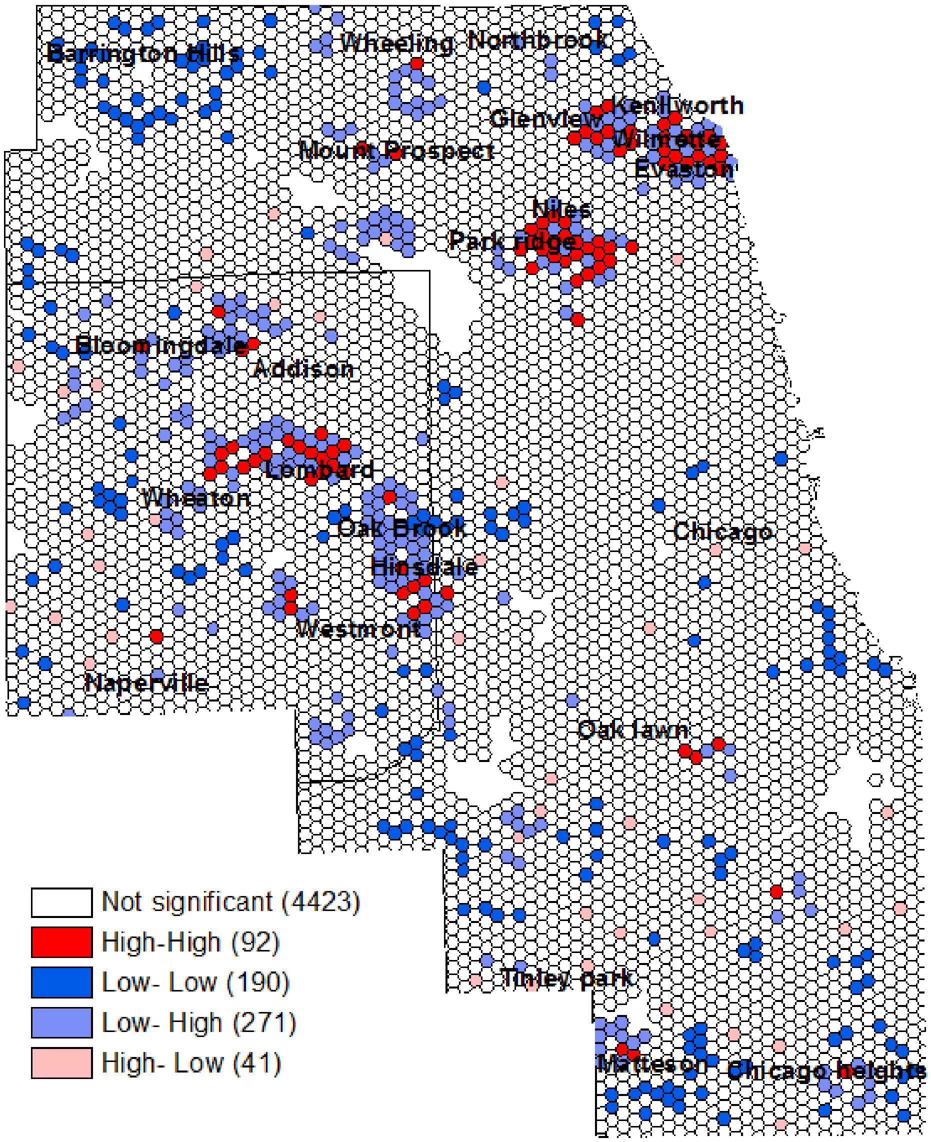

Figure 5.5. The local Moran's I result showing the spatial clustering of cumulative human WNV infections from 2005- 2016 in Cook and DuPage Counties, Illinois.

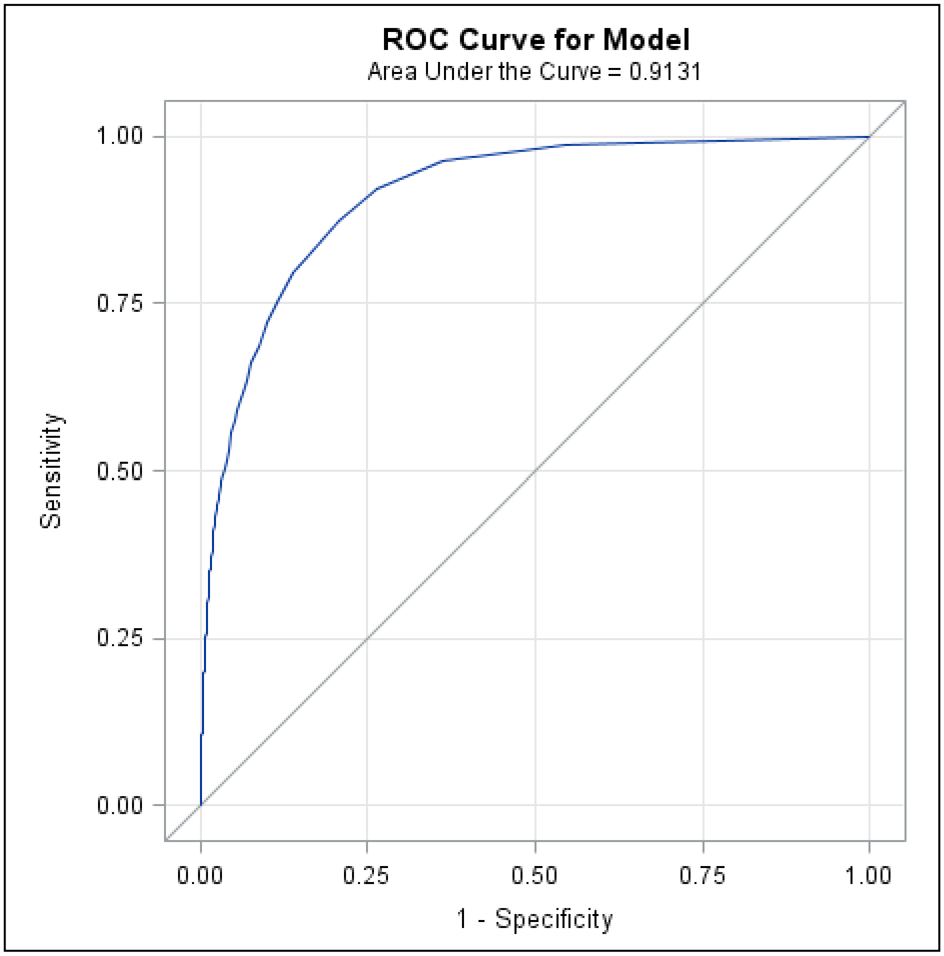

Figure 5.6. The receiver operating characteristics (ROC) curve for the final model.

Table 5.1. List of explanatory variables.

S.N.	Variables	Notation	S.N.	Variables	Notation
	Landscape			Weather	
A	Land cover		C	Temperature	
1	Proportion of developed open space	dospct	1	Average temperature of one week before	templag1
2	Proportion of developed low intensity	dlipct	2	Average temperature of two weeks before	templag2
3	Proportion of developed medium intensity	dmipct	3	Average temperature of three weeks before	templag3
4	Proportion of developed high intensity	dhipct	4	Average temperature of four weeks before	Templag4
5	Proportion of deciduous forests	dfpct	D	Precipitation	
6	Proportion of evergreen forests	efpct	1	Average precipitation of one week before	precilag1
7	Proportion of mixed forests	mfpct	2	Average precipitation of two weeks before	precilag2
8	Proportion of barren land	blpct	3	Average precipitation of three weeks before	precilag3
9	Proportion of shrubs	shrubspct	4	Average precipitation of four weeks before	precilag4
10	Proportion of grassland	glandpct	E	Demographic factors	
11	Proportion of pasture	pasturepct	1	Percentage of White population	whitepct
12	Proportion of cultivated land	clpct	2	Percentage of African American	blackpct
13	Proportion of woody wetlands	wwpct	3	Percentage of Asian population	asianpct
14	Proportion of herbaceous wetlands	hwpct	4	Percentage of Hispanic	hispanicpct
15	Proportion of open water	owpct	5	Median household income	income
B	Mosquito infection rate				
1	Mosquito infection of one week before	mirlag1			
2	Mosquito infection of two weeks before	mirlag2			
3	Mosquito infection of three weeks before	mirlag3			
4	Mosquito infection of four weeks before	mirlag4			

Table 5.2. Annual human WNV cases, average seasonal mosquito infection rate (MIR), and mosquito testing from 2005 to 2016 in Cook and DuPage counties.

Year	Number of human cases	Average MIR	Number of pools tested	Number of positive pools	Total number of mosquitoes tested
2005	181	5.33	7,165	1,939	271,235
2006	129	5.35	9,428	1,984	318,386
2007	43	2.65	12,131	1,259	375,520
2008	10	1.91	9,024	587	298,995
2009	1	1.14	9,450	298	311,220
2010	47	5.19	11,491	2,086	393,279
2011	24	3.10	8,911	939	287,774
2012	229	7.35	10,162	3,182	323,497
2013	66	4.26	11,078	1,967	407,326
2014	31	2.97	9,273	990	333,489
2015	36	3.57	7,725	1,046	314,363
2016	108	6.34	6,144	1,687	219,909

MIR= Mosquito infection rate; WNV= West Nile virus

Table 5.3. Spearman correlation of weekly cumulative human WNV cases and lagged MIR for all years, high and low years from 2005- 2016 in Cook and DuPage Counties.

		Human WNV cases		
MIR	All years	High years	Low years	Year 2012
Same week	0.776	0.775	0.671	0.818
One week before	0.837	0.884	0.737	0.899
Two weeks before	0.765	0.766	0.698	0.875
Three weeks before	0.601	0.574	0.556	0.727
Four weeks before	0.429	0.354	0.394	0.501
Five weeks before	0.289	0.147	0.286	0.283
Six weeks before	0.142	0.001	0.120	0.038

MIR= Mosquito infection rate; WNV= West Nile virus

Table 5.4. The regression equations of the relationship between a cumulative number of WNV positive pools, mosquito infection rate in a six-week period early and mid-summer and human West Nile virus illnesses for the year for Cook and DuPage Counties from 2004- 2014.

Week	Regression equation	R-square	PRESS Statistics
28	30.1 + 0.445 * Number of positive pools	0.721	145016
29	21.2 + 0.278 * Number of positive pools	0.825	54037
30	11.8 + 0.194 * Number of positive pools	0.895	23331
31	2.33 + 0.144 * Number of positive pools	0.931	9096.78
32	- 6.0 + 0.118 * Number of positive pools	0.917	7355.94
33	- 16.5 + 0.103 * Number of positive pools	0.901	7299.26
34	- 23.7 + 0.0938 * Number of positive pools	0.863	9757.17
35	- 29.5 + 0.0861 * Number of positive pools	0.813	13859.4
Early summer MIR (Week 22- 27)	13.7 + 162 * average MIR of week 22- 27	0.833	29238.5
Mid-summer MIR (Week 28- 33)	- 16.7 + 14.7 * average MIR of week 28- 33	0.936	4891.55

Table 5.5. Candidate models for predicting the probability of human WNV occurrence using weather, land cover, mosquito infection, and demographic factors in Chicago region.

Model	Variables included	K	-2 log likelihoods	AIC	ΔAIC
1	Yr + templag2- 4 + precilag2 + mirlag1- 4 + whitepct + owpct + dmipct + dhipct	14	12480.5	12530.5	0
2	Yr + templag2- 4 + precilag2 and 4 + mirlag1- 4 + whitepct + owpct + dmipct + dhipct	15	12484.1	12536.1	5.6
3	Yr + templag2- 4 + mirlag1- 4 + whitepct + owpct + dmipct + dhipct	13	12489.3	12537.3	6.8
4	Yr + templag2- 4 + precilag2 + mirlag1- 4 + whitepct + dmipct + dhipct	13	12490.8	12538.8	8.3
5	Yr + templag2- 4 + precilag2 and 4 + mirlag1- 4 + whitepct + income + owpct + dmipct + dhipct	16	12488.7	12542.7	12.2
6	Yr + templag1- 4 + precilag2 and 4 + mirlag1- 4 + income + whitepct + owpct + dmipct + dhipct	17	12503.5	12559.5	29
7	Yr + templag1- 4 + precilag1-2 and 4 + mirlag1- 4 + income + whitepct + owpct + dmipct + dhipct	18	12502.6	12560.6	30.1
8	Yr + templag1- 4 + precilag1- 4 + mirlag1- 4 + income + whitepct + owpct + dmipct + dhipct + mfpct + glandpct + wwpct	22	12502.6	12560.6	30.1
9	Global model (all predictor variable included)	33	12476.47	12566.5	36
10	Null model	1	14210.7	14214.7	1684.2

Table 5.6. Model parameters for the best model using weather, land cover, mosquito infection, and demographic factors to predict the occurrence of WNV human cases in Chicago region.

Variable	Parameter estimate	F-value	P-Value	Odds ratio (95% CI)
Fixed effects				
Year	-	15.53	<0.001	-
Temperature of two weeks before	0.0771	26.64	<0.001	1.08 (1.049 -1.112)
Temperature of three weeks before	0.1202	53.32	<0.001	1.128 (1.092- 1.165)
Temperature of four weeks before	0.1799	137.39	<0.001	1.197 (1.162- 1.234)
Precipitation of two weeks before	-0.0026	3.03	0.081	0.0997 (0.994- 1)
Mosquito infection rate of one week before	0.0028	17.30	<0.001	1.003 (1.002- 1.004)
Mosquito infection rate of two weeks before	0.00375	35.37	<0.001	1.004 (1.002- 1.005)
Mosquito infection rate of three weeks before	0.00378	35.83	<0.001	1.004 (1.002- 1.005)
Mosquito infection rate of four weeks before	0.00377	34.97	<0.001	1.004 (1.002- 1.005)
White population percentage	0.0089	34.73	<0.001	1.009 (1.006- 1.012)
Open water percentage	-0.0474	6.97	0.008	0.954 (0.921- 0.988)
Developed medium intensity	-0.0105	23.87	<0.001	0.990 (0.985- 0.994)
Developed high intensity	-0.0147	30.15	<0.001	0.985 (0.980- 0.991)
Random effect				
Subject	Estimate	Standard error	Z-value	P-value
Hexagon ID	0.735	0.133	5.50	<0.0001

CHAPTER 6: CONCLUSIONS, RECOMMENDATIONS, AND FUTURE DIRECTIONS

In this dissertation research, we evaluated key components associated with the risk of mosquito-borne disease transmission to humans. The three major components we considered were *Culex* abundance, WNV mosquito infection, and human WNV illness. Specifically, we examined different biotic and abiotic factors that could potentially drive *Culex* vector mosquito abundance, mosquito infection rate, and human WNV illness in Illinois. For this, we used long-term mosquito abundance and mosquito testing data collected intensively by our research group in South Cook County, Illinois, and long-term mosquito testing data and point-level data for human WNV cases across Illinois from the Illinois Department of Public Health, which we obtained through a user agreement. Additionally, we collated freely available weather, land cover, and demographic information from different sources. We applied different statistical, landscape, and geospatial modeling approaches to identify the factors associated with mosquito abundance, mosquito infection, and human WNV illness.

We found that the weather variables temperature, precipitation, wind speed, and humidity were driving the weekly variation in the estimates of *Culex* vector abundance in a suburban environment of Chicago, with differences in the strength and direction of association being observed depending upon the mosquito trapping methods used. The local landscape condition also affected the mosquito abundance, with more mosquitoes found in the semi-natural areas compared to residential areas in suburban Chicago. We extended our initial study of mosquito abundance and used a multilevel modeling approach to consider both weather and landscape variables simultaneously to better understand the drivers of mosquito abundance in a suburban environment. We found that the dynamics of mosquito populations are mainly driven by the weekly variation in the weather conditions, but local landscape structure is also an important contributor. Most interestingly, and contrary to our expectation, we found fewer *Culex* mosquitoes near urban catch basins, a structure designed to manage urban run-off which is used by mosquitoes as one of their breeding grounds.

In a separate study, we developed prediction models for the WNV mosquito infection rate using the prior weeks and seasonal weather data for the state of Illinois and it's nine climate divisions. We found the MIR model worked better for northeast Illinois where robust data on mosquito testing were observed but poorly performed for southern part of the state, where mosquito testing data were sparse. In the same study, we also found that the occurrence of human WNV cases was preceded by several weeks of positive mosquito pools. We categorized the weeks into high, medium, and low risk depending upon the threshold of the observed MIR.

In the final study, we evaluated the weather, land cover, demographic, and mosquito infection data to understand the fine-scale drivers of spatiotemporal variability of human WNV cases in Chicago region. We identified higher temperature and MIR of the preceding weeks, and relatively low rainfall two weeks before was mainly driving the spatiotemporal variability of human WNV occurrence in Chicago region. We also found that medium and high-intensity urban areas in Chicago were at lower risks for having a WNV case compared to suburban areas. Further, we identified a strong temporal correlation between the weekly lagged MIR and human cases, with the strength of correlation differing between high and low WNV years. We also found that either the mid-summer average MIR or the cumulative mosquito positive pools as early as week 31 (July end) could fairly predict the total annual human WNV cases.

The comparison of mosquito abundance, mosquito infection, and human illness models in terms of their association with weather and landscape variables yielded some coherent and some conflicting results. For example, in general the higher temperatures of preceding weeks were associated with higher mosquito abundance, higher mosquito infection, and increased probability of having a WNV human case. However, the relationship with precipitation was not as coherent as with temperature. The higher precipitation in earlier weeks resulted in increased *Culex* abundance but it was not true for either mosquito infection or human illness. In contrast, we found that there was a higher probability of having a human WNV case when earlier weeks precipitation was lower. For mosquito infection, the seasonal precipitation and interaction with temperature appeared to be more important than the preceding weeks precipitation alone. This indicates that higher precipitation may result in higher number of mosquitoes but not necessarily higher infection rate or increased probability of human infection. A direct comparison of mosquito abundance with mosquito infection and human WNV illness might help address this issue which was not possible in this study due to the absence of mosquito abundance data across Illinois. The difference in the spatial scales used in different models might also have contributed to some of the observed discrepancies. In terms of land cover variables, higher numbers of mosquitoes were found near the water bodies (in light traps) but we found decreased probability of having a WNV case of illness when there was a higher proportion of water bodies in an area. The differences in the flight range of mosquitoes and human movement pattern might affect these relationships. Further, we do not exactly know where a person picks up the infection. Overall, it is difficult to make direct comparison between the mosquito abundance and human WNV model due to the differences in the spatial scales and variables used to develop the model. The evaluation of mosquito abundance, mosquito infection, and human WNV illness using the same sets of weather and land cover variables in the same spatial scale might help explain some of the discrepancies we observed in our studies.

Based on our findings, we suggest using a combination of trapping methods to get a better picture of mosquito abundance in any area, as abundance estimates obtained from only one type of trap may not truly represent the underlying mosquito abundance. Also, we recommend evaluating the landscape features surrounding the catch basins to evaluate if there are suitable features to support mosquito population or the observance of fewer *Culex* was due to the success of mosquito control activities going on in the area. To improve the weekly MIR prediction model, we suggest incorporating the local landscape conditions, which may help to explain some of the uncertainties in the model unexplained by weather alone.

From a public health perspective, the knowledge we gained from our modeling approach can be tested in the field collaborating with local public health agencies and tailoring the model based on their local data. Also, it would be helpful to automate our modeling approach so that it can be made more accessible to the agencies working in mosquito control, other researchers, and the public. For the areas where mosquito testing data are sparse, we suggest additional review is needed to determine where to increase the mosquito surveillance activities so that better prediction models for the future can be generated for those areas. Other places may actually require less surveillance to deliver a similar result. Also, considering the limitation of the mosquito infection rate due to its susceptibility to the number of mosquitoes tested, it would be worth to concurrently use other alternative measures such as the number of positive pools. One limitation we observed while using the data from the IDPH was that the mosquito abundance measures are not included in these data. If abundance data corresponding to mosquito testing were available, we could better develop a risk index measure known as the vector index to estimate the risks for human WNV occurrence. Other states, for example, have long-term trapping efforts to measure mosquito populations across the state, and Illinois would be well served by such a system (Barker et al., 2003; Anderson et al., 2011; Dunphy et al., 2014). We also suggest evaluating the spatiotemporal variability of human WNV risk beyond 1000m hexagons and testing them at different spatial scales, which may help to better understand the geographic scales at which these processes occur at the local level. It would also be helpful to include seasonal weather variables, and see if they affect the model. Also, we recommend evaluating neuroinvasive and non-neuroinvasive cases separately in the future study. These severe cases are considerably less prone to reporting bias (Petersen et al., 2013a).

One of the important considerations for the future study would be to consider the climate change scenario, as mosquito-borne diseases are directly related to the weather conditions. Projected climate change scenarios have estimated that the temperature would increase, and the precipitation pattern will vary with some experiencing higher rainfall, and some areas experiencing increased drought. Several studies have estimated that there would be an increase in the occurrence of mosquito-borne diseases, including WNV in the future (Harrigan et al., 2014; Paull et al., 2017). The prediction model we have developed for mosquito and human WNV infection can be tested using different climate scenarios to evaluate how these are going to vary in Illinois. This will give public health agencies an opportunity to better prepare themselves for the upcoming challenges. Also, with the recent Zika emergence in South America, and some locally acquired Zika cases already in some states of USA, the surveillance of *Aedes* mosquitoes needs to be taken into consideration. Some of the techniques and approaches we developed during this dissertation research can be extrapolated and used for other mosquito-borne diseases, including Zika.

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APPENDIX A: SUPPLEMENTARY MATERIALS FOR CHAPTER 4

FIGURES AND TABLES

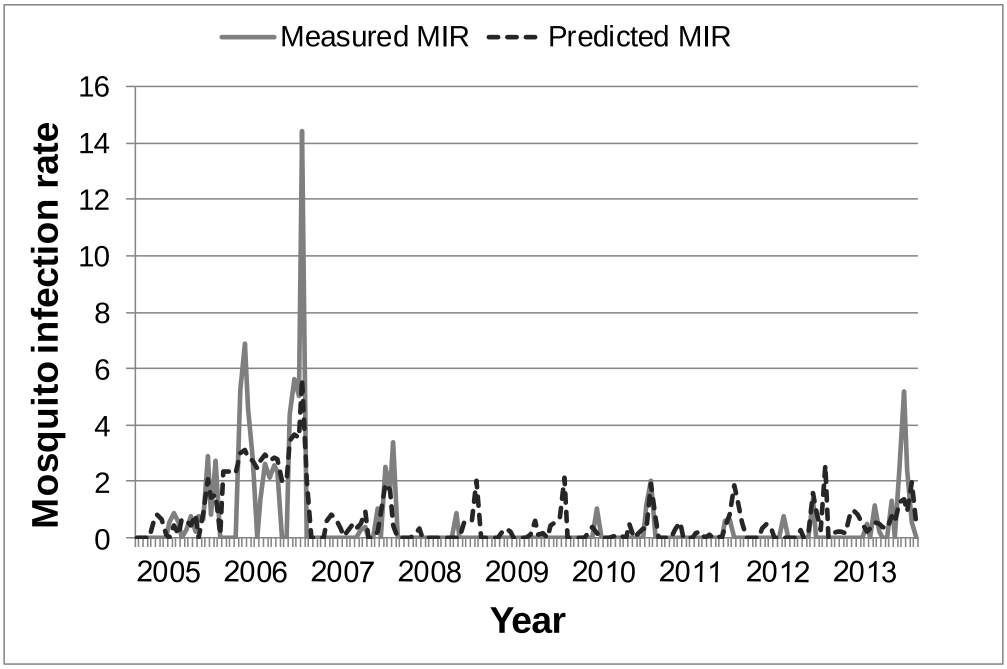

Figure A.1. Measured (solid) and predicted (dotted) mosquito infection rate in climate division 1 (Northwest Illinois) during summer season (weeks 18 to weeks 38).

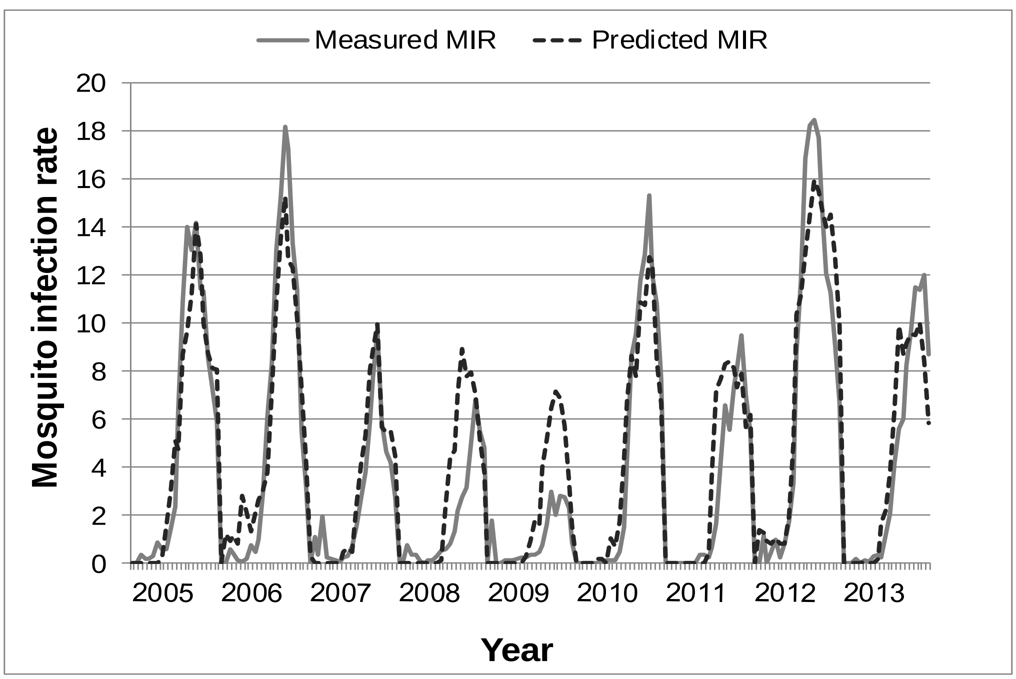

Figure A.2. Measured (solid) and predicted (dotted) mosquito infection rate in climate division 2 (Northeast Illinois) during summer season (weeks 18 to weeks 38).

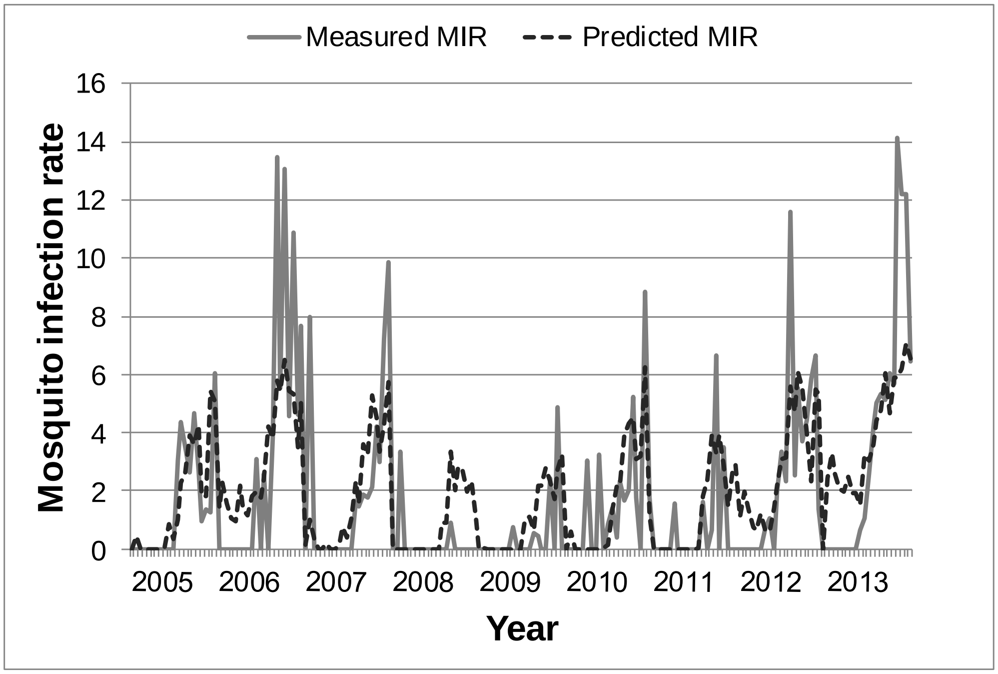

Figure A.3. Measured (solid) and predicted (dotted) mosquito infection rate in climate division 4 (Central Illinois) during summer season (weeks 18 to weeks 38).

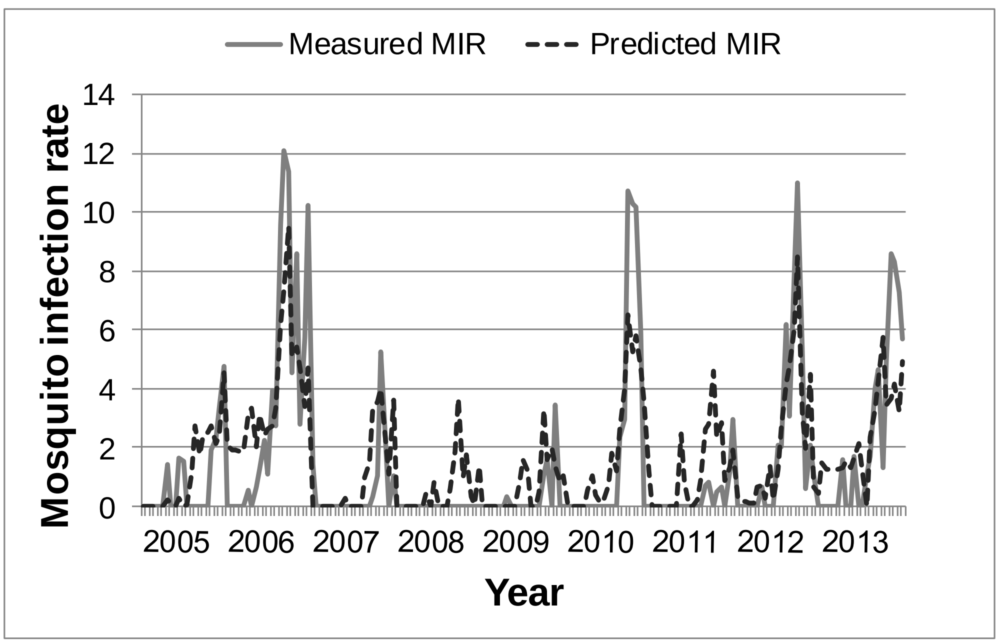

Figure A.4. Measured (solid) and predicted (dotted) mosquito infection rate in climate division 5 (East Illinois) during summer season (weeks 18 to weeks 38).

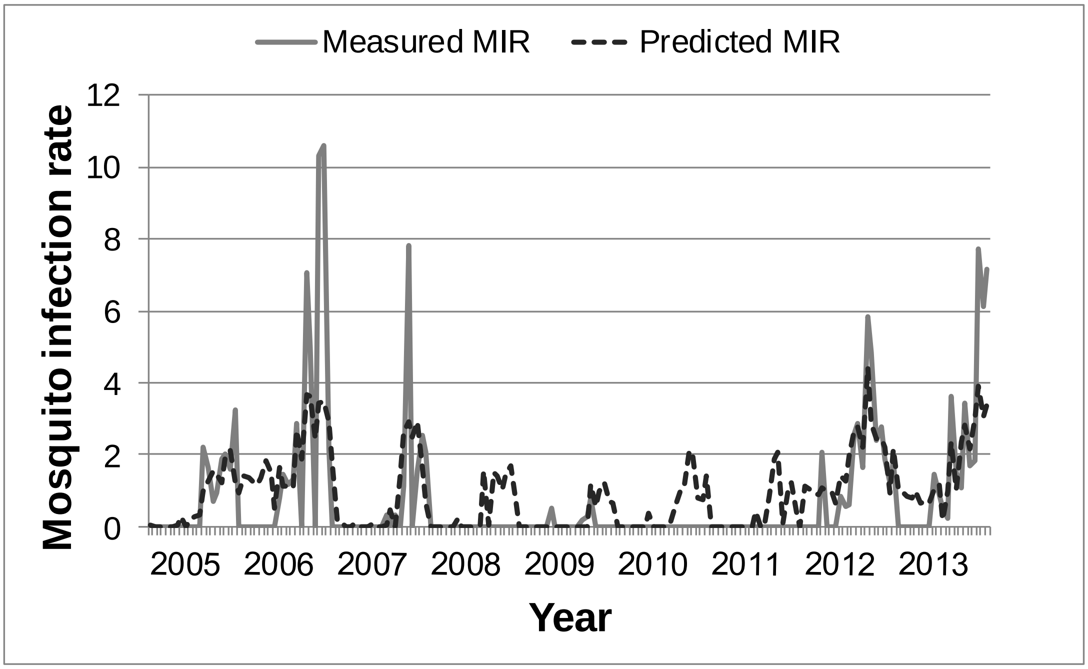

Figure A.5. Measured (solid) and predicted (dotted) mosquito infection rate in climate division 6 (West southwest) during summer season (weeks 18 to weeks 38).

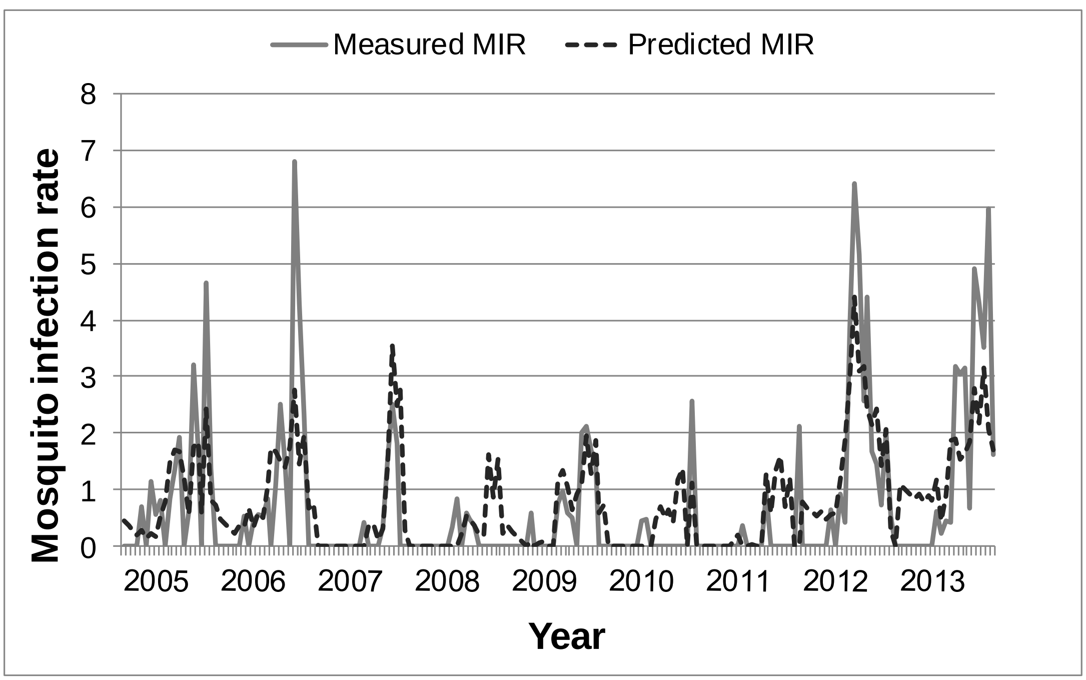

Figure A.6. Measured (solid) and predicted (dotted) mosquito infection rate in climate division 8 (Southwest) during summer season (weeks 18 to weeks 38).

Table A.1. Independent variables considered in the model development.

Variables	Abbreviation
Weekly lagged temperature of previous week (lag1)	dwlag1
Weekly lagged temperature of 2 weeks back (lag2)	dwlag2
Weekly lagged temperature of 3 weeks back (lag3)	dwlag3
Weekly lagged temperature of 4 weeks back (lag4)	dwlag4
Weekly lagged precipitation of previous week (lag1)	precilag1
Weekly lagged precipitation of 2 weeks back (lag2)	precilag2
Weekly lagged precipitation of 3 weeks back (lag3)	precilag3
Weekly lagged precipitation of 4 weeks back (lag4)	precilag4
Length of daylight hours	daylighthours
Interaction between length of daylight hours and temperature lag 1	daylighthoursdw1
Interaction between weekly temperature and precipitation lag1	dw1preci1
Interaction between weekly temperature and precipitation lag2	dw1preci2
Interaction between weekly temperature and precipitation lag3	dw1preci3
Interaction between weekly temperature and precipitation lag4	dw1preci4
Interaction between weekly temperature lag2 and precipitation lag1	dw2preci1
Interaction between weekly temperature lag2 and precipitation lag2	dw2preci2
Interaction between weekly temperature lag2 and precipitation lag3	dw2preci3
Interaction between weekly temperature lag2 and precipitation lag4	dw2preci4
Interaction between weekly temperature lag3 and precipitation lag1	dw3preci1
Interaction between weekly temperature lag3 and precipitation lag2	dw3preci2
Interaction between weekly temperature lag3 and precipitation lag3	dw3preci3
Interaction between weekly temperature lag3 and precipitation lag4	dw3preci4
Interaction between weekly temperature lag4 and precipitation lag1	dw4preci1
Interaction between weekly temperature lag4 and precipitation lag2	dw4preci2
Interaction between weekly temperature lag4 and precipitation lag3	dw4preci3
Interaction between weekly temperature lag4 and precipitation lag4	dw4preci4
Abnormal average temperature of spring (wks 10-22) of same year	springtemp
Seasonal average temperature of winter	wintertemp
Seasonal average temperature of last fall	lastfalltemp
Seasonal average temperature of last summer	lastsummertemp
Seasonal average temperature of last spring	lastspringtemp
Seasonal total precipitation of spring (wks 10-22) of same year	springpreci
Seasonal total precipitation of winter	winterpreci
Seasonal total precipitation of last fall	lastfallpreci
Seasonal total precipitation of last summer	lastsummerpreci
Seasonal total precipitation of last spring	lastspringpreci

Spring: March to May (weeks 10-22), Summer June to August (weeks 23-35), Fall: September to November (weeks 36-48), Winter: December to February (weeks 49- 9).

Table A.2. Monthly average number of mosquito pools tested from 2005 to 2013 by climate divisions in Illinois.

	May	June	July	August	September
Climate division	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
CD 1 (Northwest)	2.0 (7.0)	29.0 (17.4)	43.4 (14.4)	35.2 (15.9)	27.4 (14.6)
CD 2 (Northeast)	148.5 (110.9)	534.4 (162.7)	761.4 (184.4)	709.8 (140.6)	494.7 (114.7)
CD 3 (West)	1.2 (2.8)	12.6 (7.3)	16.5 (9.5)	11.9 (8.4)	5.4 (5.1)
CD 4 (Central)	7.8 (9.6)	33.5 (15.1)	45.6 (17.5)	45.5 (21.7)	31.8 (24.9)
CD 5 (East)	30.5 (29.0)	43.0 (23.3)	47.8 (33.2)	40.7 (24.2)	34.6 (20.3)
CD 6 (West southwest)	3.7 (5.9)	20.6 (12.0)	31.6 (12.2)	30.8 (12.0)	20.3 (10.6)
CD 7 (East southeast)	0.2 (1.1)	3.6 (5.8)	9.2 (10.7)	4.7 (5.1)	3.9 (6.0)
CD 8 (Southwest)	8.4 (9.9)	31.6 (10.8)	32.8 (11.2)	30.7 (11.3)	21.1 (10.1)
CD 9 (Southeast)	3.3 (3.4)	7.9 (3.9)	9.2 (5.7)	9.2 (5.7)	6.2 (4.8)

*SD=Standard deviation

Table A.3. Correlation of weekly mosquito infection rate and number of human cases the same week and one to two weeks later.

		Number of human cases		
Regions	N*	Same week (p-value)	One week after (p-value)	Two weeks after (p-value)
Illinois	210	0.772 (<0.0001)	0.779 (<0.0001)	0.787 (<0.0001)
CD01	210	0.259 (0.0001)	0.361 (<0.0001)	0.259 (0.0001)
CD02	210	0.792 (<0.0001)	0.817 (<0.0001)	0.821 (<0.0001)
CD03	210	0.049 (0.47)	0.061 (0.37)	0.057 (0.41)
CD04	210	0.373 (<0.0001)	0.394 (<0.0001)	0.326 (<0.0001)
CD05	210	0.328 (<0.0001)	0.379 (<0.0001)	0.324 (<0.0001)
CD06	210	0.409 (<0.0001)	0.341 (<0.0001)	0.432 (<0.0001)
CD07	210	0.094 (0.17)	0.241 (0.0004)	0.063 (0.36)
CD08	210	0.255 (0.0002)	0.247 (0.0003)	0.318 (<0.0001)
CD09	210	0.121 (0.07)	0.214 (0.001)	0.242 (0.0004)

*N= Number of weeks

Table A.4. The number of weeks with measured values of MIR at seven classes of severity and the number and percentage of human cases that followed during the summer month from 2004 to 2013 for the state of Illinois.

	Weeks			Human cases one week after		
MIR	Number	Percentage	Cumulative percentage	Number	Percentage	Cumulative percentage
>5	12	5.7	5.7	352	31.8	31.7
4.01 to 5	1	0.5	6.2	28	2.5	34.3
3.01 to 4	16	7.6	13.8	211	19.1	53.3
2.01 to 3	21	10.0	23.8	267	24.1	77.5
1.01 to 2	31	14.8	38.6	163	14.7	92.2
0.01 to1	103	49.0	87.6	86	7.8	100
0	26	12.4		0	0	
Total	210		100%	1107		100%

Table A.5. The regression equations of the relationship between average mosquito infection rate in a six-week period mid-season and human West Nile virus illnesses for the year for the state of Illinois and for each of the climate divisions.

Climate division	Regression equation	R-square	Predicted R-square
Illinois	0.1 + 60.1*MIR	0.693	0.648
Northwest (1)	2.41 + 1.70*MIR	0.034	0
Northeast (2)	-12.1 + 18.7*MIR	0.921	0.899
West (3)	0.39 + 0.29*MIR	0.062	0
Central (4)	1.20 + 1.22*MIR	0.313	0.135
East (5)	0.89 + 0.38*MIR	0.207	0.065
West southwest (6)	0.92 + 1.75*MIR	0.499	0.256
East southeast (7)	0.69 + 1.25*MIR	0.170	0
Southwest (8)	2.10 + 1.15*MIR	0.019	0
Southeast (9)	0.63 + 0.61*MIR	0.120	0

Table A.6. Parameter estimates of the weather variables for state-wide model.

Variable	Parameter estimate	SE	t Value	Pr > |t|	Standardized estimate
Intercept	2.66	1.4838	1.8	0.0744	0
dwlag1	0.209	0.049	4.19	<.0001	1.328
dwlag2	-0.135	0.06808	-1.99	0.0487	-0.8064
dwlag4	-0.069	0.03747	-1.85	0.0664	-0.3518
springtemp	0.121	0.064	1.9	0.0598	0.165
wintertemp	0.154	0.085	1.79	0.0745	0.218
lastfalltemp	-0.353	0.09496	-3.71	0.0003	-0.2707
daylightlag1	-0.175	0.10287	-1.71	0.0894	-0.1002
springpreci	0.261	0.15925	1.64	0.1034	0.16315
winterpreci	-1.159	0.25949	-4.47	<.0001	-0.3281
lastfallpreci	-1.151	0.26199	-4.39	<.0001	-0.4788
dw1preci1	-0.049	0.01629	-3.01	0.003	-0.6693
dw1preci2	0.042	0.0307	1.37	0.1735	0.59138
dw2preci2	-0.152	0.05617	-2.7	0.0077	-2.0436
dw2preci3	0.086	0.03553	2.42	0.0168	0.72676
dw2preci4	-0.095	0.04025	-2.35	0.02	-0.813
dw3preci2	0.151	0.04824	3.13	0.0021	1.85465
dw3preci3	-0.167	0.05682	-2.94	0.0038	-1.2517
dw3preci4	0.096	0.04384	2.19	0.03	0.74915
dw4preci1	0.061	0.02013	3.02	0.0029	0.69428
dw4preci2	-0.052	0.02158	-2.44	0.0156	-0.5568
dw4preci3	0.074	0.03558	2.07	0.0401	0.50294

*SE= Standard error

Table A.7. Standardized parameter estimates of the weather variables for different climate regions.

Variables	CD01	CD02	CD04	CD05	CD06	CD08
Intercept	0	0	0	0	0	0
dwlag1	-2.93	1.261	0.532	1.003	-	-
dwlag2	-	-	-	-	-0.850	-
dwlag3	0.629	-0.905	-	-0.730	-	-
dwlag4	-	-	-0.448	-	-	-0.329
springtemp	1.053	-	0.187	-0.736	-	-
wintertemp	-0.766	0.231	-	-	0.282	0.820
lastfalltemp	0.829	-0.35	-0.127	-	-	-0.358
lastsummertemp	-	-	-	-0.197	-	-0.437
lastspringtemp	0.565	-0.402	0.186	-0.283	-	-
precilag1	-	0.102	-	-	-	-
precilag2	-	-	-	-	-	-
precilag3	-	-	-	-	-	-
precilag4	-	-	-	-	-	-
springpreci	0.246	-	0.177	-0.583	-	0.760
winterpreci	-	-	-0.161	-0.466	-0.193	-0.137
lastfallpreci	-1.167	-0.503	-0.385	-0.482	-0.187	0.376
lastsummerpreci	-	-	-		-	-
lastspringpreci	-	-	-	-	-	-
daylightlag1	-	-	-0.138	-	-0.134	-0.187
dw1daylightlag1	2.312	-	-	-	0.933	0.310
dw1preci1	-	-0.321	-	-	-	-1.504
dw1preci2	-0.534	-	-	-	-	-
dw1preci3	-	0.985	-	-	-	-
dw1preci4	-	-0.791	-0.454	-	-	-
dw2preci1	-	-	-	-	-	1.451
dw2preci2	0.637	-0.132	-	-0.228	-0.972	-2.359
dw2preci3	-	-1.048	-	0.905	-	-
dw2preci4	-	0.719	-	-	-	-0.663
dw3preci1	-	-	-	-	1.482	-
dw3preci2	-	-	-	-	-	2.244
dw3preci3	-	-	-	-1.575	-	-
dw3preci4	-	-	0.554	0.514	-	0.615
dw4preci1	-	0.129	-	-	-1.502	-
dw4preci2	-	-	-0.164	-	1.008	-
dw4preci3	-0.127	-	-	0.665	-	-
dw4preci4	-	-	-	-0.468	-	-